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The Western Journal of Medicine

VOLUME 149 • NUMBER 4 OCTOBER 1988

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IN HYPERTENSION*

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***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

---

1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.

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WARNINGS: Neutropenia/Agranulocytosis—Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension—Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

ARMY RESERVE MEDICAL PROFILE NO.7

Soldier being examined for effects of high-altitude cerebral edema.

ALLAN J. HAMILTON, M.D.

Neurosurgical Resident and Research Fellow, Massachusetts General Hospital, Boston, Massachusetts. Captain, U.S. Army Reserve.

EDUCATION Ithaca College, B.A. (Magna Cum Laude); Hamilton College (Pre-med); Harvard Medical School.

RESIDENCY General Surgical Internship. Neurosurgical Residency, Massachusetts General Hospital.

CONTINUING EDUCATION Neurology and Neurosurgery Research Fellowship Training, National Institutes of Health.

OUTSTANDING ACHIEVEMENTS Olsen Memorial Fellowship, National Masonic Medical Research Foundation; Albert Schweitzer Fellowship, International Albert Schweitzer Foundation; Harvard Medical School Cabot Prize for Best Senior Thesis; recently published article, "Who Shall Live and Who Shall Die" in Newsweek Magazine.

"The work I'm doing in the Army Reserve fits perfectly with my academic research interests in civilian life. The Army is very concerned with the effects of high-altitude cerebral edema, which is a mirror model of cerebral hypoxia, something I deal with every day in our neurosurgical intensive care unit. I couldn't ask for a smoother transition. And that's true for a lot of Reserve physicians. All we really do is change our clothes, not our mindset.

"Some of the projects the Army is undertaking are on the cutting edge of research. For example, I'm currently involved in developing for the Army a prototype of a non-invasive intracranial pressure-monitoring device that we hope will allow us to measure pressure changes as the brain swells—without drilling holes in the skull. If we can get our design to work, such a device could revolutionize high-altitude medicine as well as civilian neurosurgical care.

"The quality of medicine and the caliber of people I've been associated with in the Army Reserve are, without question, equal to civilian hospitals. In fact, I'm giving serious consideration to applying for an active duty academic position in Army Medicine when my residency ends at Massachusetts General."

Find out more about the medical opportunities in the Army Reserve. Call toll free 1-800-USA-ARMY.

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Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 21-23—**Diagnosis and Management of Respiratory Diseases.** The Boulders, Scottsdale. Fri-Sun. Contact: Medical Education Resources, 1 (800) 421-3756.

October 28—**Conference on Cancer Pain Management.** DuVal Auditorium, University of Arizona Health Sciences Center, Tucson. Fri. Contact: U of A.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

November 10-12—**First Annual Spinal Workshop.** The Pointe at Squaw Peak, Phoenix. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1.

November 11-13—**17th Annual Seminar—Musculoskeletal Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Department of Radiology, Maricopa Medical Center, (602) 267-5361.

December 3-4—**Annual Meeting of the Arizona Chapter of the American College of Surgeons.** Rancho de los Caballeros, Wickenburg. Sat-Sun. Contact: Lee Ansel, MD, Program Chairman, (602) 251-3131.

January 13-14—**Geriatrics in a Changing Society.** Scottsdale. Fri-Sat. Contact: Jean Kiernat, Institute of Gerontology, (602) 239-5844.

January 27-29—**Mammography and the Search for Breast Cancer.** Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Tess Wade, Breast Clinic of Rochester, (716) 442-8969.

February 22-24—**12th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Phoenix OB/GYN Society, (602) 266-6321.

February 28-March 3—**Pediatric Update 1989.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Barbara Bengtson, Phoenix Children's Hospital, (602) 239-4350.

March 4-8—**Third Annual Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, Barrow Neurological Institute, (602) 285-3956.

March 9-11—**Current Management of Central Nervous System Tumors.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, (602) 285-3178 or 1-800-BARROW-1.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

November 10—**Advances in Diagnosis and Treatment of Allergic Diseases.** UCSF at Le Meridien Hotel, San Francisco. Thurs. 8 hrs. $100. Contact: UCSF.

ANESTHESIOLOGY

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologist at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 29-February 3—**Clinical Update in Anesthesiology.** Tucson Hospitals Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray G. Atnikov, MD, c/o Box F110-63, Blaine, WA 98230. (604) 874-5291.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sat-Sun. Contact: Murray G. Atnikov, MD. (604) 874-5291.

CARDIOLOGY

October 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt on Union Square, San Francisco. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

EMERGENCY MEDICINE

October 21-23—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

November 4-6—**Management of the Child With Head Injury.** Children's Hospital Oakland at Monterey Conference Center and Hotel Pacific, Monterey. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, Continuing Medical Education, Children's Hospital Oakland, 747-52nd St, Oakland 94609. (415) 428-3021.

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CEDARS-SINAI ANNOUNCES A NEW, STATE-OF-THE-ART BILIARY DISEASE CENTER.

Cedars-Sinai Biliary Disease Center is a comprehensive new center offering a full range of non-surgical treatments for symptomatic gallstones. Some, such as oral bile acids, are already in general use; others, such as biliary lithotripsy and MTBE perfusion are currently under study.

If surgery is recommended, special techniques in intraoperative imaging are available in the medical center's operating rooms. If you have patients with symptomatic gallstones, call the Biliary Disease Center for an informational brochure. (213) 855-3581 or (800) 442-4999.

THE BILIARY DISEASE CENTER
CEDARS-SINAI MEDICAL CENTER
8700 Beverly Boulevard, Los Angeles, CA 90048

CONTINUING MEDICAL EDUCATION

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November 7-10—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Imperial Palace, Las Vegas, Nevada. Mon-Thurs. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

November 14-18—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III & Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 4-9—**Current Concepts in Emergency Care.** Institute for Emergency Medical Education at Royal Lahaina Resort, Maui, Hawaii. Sun-Fri. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. (800) 524-5264.

December 5-9—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

January 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. $450. Contact: UCSD.

January 26-30—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Maui Marriott, Maui, Hawaii. Thurs-Mon. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

January 27-29—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

February 19-24—**Emergency Medicine.** UCD. Sun-Fri. Contact: UCD.

March 2-5—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Sheraton Universal, Los Angeles. Thurs-Sun. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

March 20-24—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. $450. Contact: UCSD.

May 1-5—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

October 15—**Current Issues in Rheumatology.** Sutter Health at Sacramento Board of Realtors Building. Sat. 4 hrs. $40. Contact: Continuing Medical Education, 1111 Howe Ave, Ste 155, Sacramento 95825. (916) 922-6568.

November 3-5—**New Directions in Anti-viral Chemotherapy.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. $100. Contact: UCSF.

November 4—**Update in Cancer Management.** Sutter Health at Sacramento Hyatt Regency. Fri. 7 hrs. $70. Contact: Continuing Medical Education, 1111 Howe Ave, Ste 155, Sacramento 95825. (916) 922-6568.

November 7-9—**12th Annual Cancer Symposium.** Scripps Memorial Cancer Hospital at Sheraton Harbor Island Hotel E, San Diego. Mon-Wed. 21 hrs. $390. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

November 9—**Gastroenterology Symposium.** Enloe Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, Medical Staff. (916) 891-7300, ext 7375.

November 11-14—**The Spine: Current Concepts of Diagnosis and Treatment.** The Spine Study Group at Marriott Desert Springs Resort, Palm Springs. Fri-Mon. $250. Contact: The Spine Study Group, PO Box 33185, San Diego 92103. (619) 692-9115.

November 16—**Common Musculoskeletal Problems.** VA Medical Center Sepulveda. 6 hrs. Contact: Arun J. Mehta, Rehabilitation Medicine Service (117), VA Medical Center, Sepulveda 91343. (818) 891-2473.

December 1-2—**Recent Advances in Occupational Cancer.** UCSF at Hotel Meridien, San Francisco. Thurs-Fri. $220. Contact: UCSF.

December 30-January 8—**Medical Acupuncture for Physicians: Part II.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. 10 days. 200 hrs. $3,200. Contact: UCLA.

January 6-7—**6th Annual Reider Laser Symposium—Urology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 19-20—**Third Urological Symposium.** Kenneth Norris Jr Comprehensive Cancer Center at Moseley-Salvatori Conference Center, Los Angeles. Thurs-Fri. 12 hrs. Contact: Louise B. Ball, Executive Secretary, PO Box J, South Pasadena 91030. (213) 680-2387.

January 23-26—**Neurology Update.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Mon-Thurs. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 25-27—**12th Annual: Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wed-Fri. 21 hrs. $400. Contact: Edith S. Bookstein, NNN, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 8-10—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort, San Diego. Wed-Fri. 21 hrs. Contact: Bonny Mower, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 20-22—**Clinical Hematology and Oncology: 1989.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, Conference Coordinator. (619) 457-8556.

(Continued on Page 404)

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December 16, 1988

Cedars-Sinai Medical Center

CONTINUING MEDICAL EDUCATION

(Continued from Page 402)

March 17-19—**Gastroenterology Update Cruise.** Center for Health Education at Queen Mary Hotel, Long Beach. Fri-Sun. Contact: Center for Health Education, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

March 21-24—**Topics in Rheumatology II.** Straub Foundation at Ilikai Hotel, Honolulu, Hawaii. Tues-Fri. 16 hrs. $350. Contact: Juliana J. Woo, MPH, Straub Foundation, 846 S Hotel St, #302, Honolulu, HI 96813. (808) 524-6755.

OB/GYN

November 11-13—**Current Issues in Perinatal Medicine.** Center for Health Education at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sun. 14 hrs. $350. Contact: Center for Health Education, 2801 Atlantic Ave, Long Beach 90701-1428. (213) 595-3811.

November 12—**Infertility Update V.** Scripps Clinic and Research Foundation Amphitheater, La Jolla. Sat. 7 hrs. $110. Contact: Bonny Mower, Box 400S, Dept of Academic Affairs, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 13-19—**11th Annual Review Course in Clinical Obstetrics & Gynecology.** The Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

November 14-15—**Gynecological Histopathology.** Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Tues. 12 hrs. $350. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

November 16-19—**Clinical Obstetrics and Gynecology.** Center for Health Education at Westin South Coast Plaza, Costa Mesa. Wed-Sat. 22 hrs. $450. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

January 6-7—**6th Annual Reider Laser Symposium—Gynecology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 29-February 2—**Ob/Gyn.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

ORTHOPEDICS

October 21-23—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, Medical Education, PO Box 84296, San Diego 92138. (619) 223-2997.

January 21-28—**Orthopaedic Emergencies.** Scripps Memorial Hospital Encinitas at Kona Surf Resort, Kona, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 12—**1989 Interim Meeting of American Orthopaedic Society of Sports Medicine.** American Orthopaedics Society for Sports Medicine at Las Vegas, Nevada. Sun. Contact: AOSSM, 70 W Hubbard St, Ste 202, Chicago, IL 60610. (312) 644-2623.

PEDIATRICS

October 15-20—**American Academy of Pediatrics Annual Session.** AAP. Sat-Thurs. Contact: AAP, 1801 Hinman Ave., Evanston, IL 60201.

October 21-22—**A Symposium on Clinical Problems in Child Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Fri-Sat. 11 hrs. $215. Contact: UCSF.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

(Continued on Page 406)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 404)

November 4-6—**Current Advances in Pediatrics.** Orange County Psychiatric Society at Disneyland Hotel, Anaheim. Fri-Sun. 14 hrs. Contact: OCPS California Chapter 4, PO Box 1297, Orange 92668. (714) 978-2415.

November 13-14—**Promoting Mental Health in Early Child Care Settings.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun-Mon. Contact: UCLA.

November 30—**Challenges in Perinatology: Are We Ready for the Future?** Perinatal Advisory Council of Los Angeles Communities at Sheraton-Universal Hotel, Universal City. Wed. 6 hrs. Contact: Marianne Gray, Executive Secretary. (213) 380-1790.

December 3—**Recent Advances in the Care of Children.** UCD at Hyatt Regency, Sacramento. Sat. 8 hrs. $125. Contact: UCD.

December 3—**7th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Educational Center, San Diego. Sat. 7 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 27-29—**27th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott. Fri-Sun. 15 hrs. $225. Contact: Katherine Barky, MD, Childrens Hospital, PO Box 54700, Los Angeles 90054.

February 10-12—**Current Concepts in Pediatric Medicine.** Children's Hospital & Health Center at Marriott Hotel, San Diego. Wed-Fri. Contact: Children's Hospital & Health Center, Continuing Medical Education Office, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 20-22—**Pediatrics Update: 1989.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

November 18-20—**34th Annual Group Therapy Symposium.** UCSF. Fri-Sun. Contact: UCSF.

January 22-27—**15th Annual Midwinter Program for Psychiatrists: Special Focus on Panic and Anxiety.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $385. Contact: UCD.

RADIOLOGY

October 31-November 4—**13th Annual San Diego Postgraduate Radiology Course.** San Diego Radiology Research and Education Foundation at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $450. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 31-November 1—**San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronada, San Diego. Mon-Tues. 28 hrs. $450. Contact: UCSD.

November 4-6—**8th Annual Interventional Course.** San Diego Radiology Research and Education Foundation at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $350. Contact: Dawn Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 13-15—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: R. Dawne Ryals, PO Box 920113, Norcross 30092-0113. (404) 641-9773.

(Continued on Page 410)

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INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

NITRO-DUR is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR therapy. If headache persists, the NITRO-DUR dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR dosage should be reduced or use of the product discontinued.

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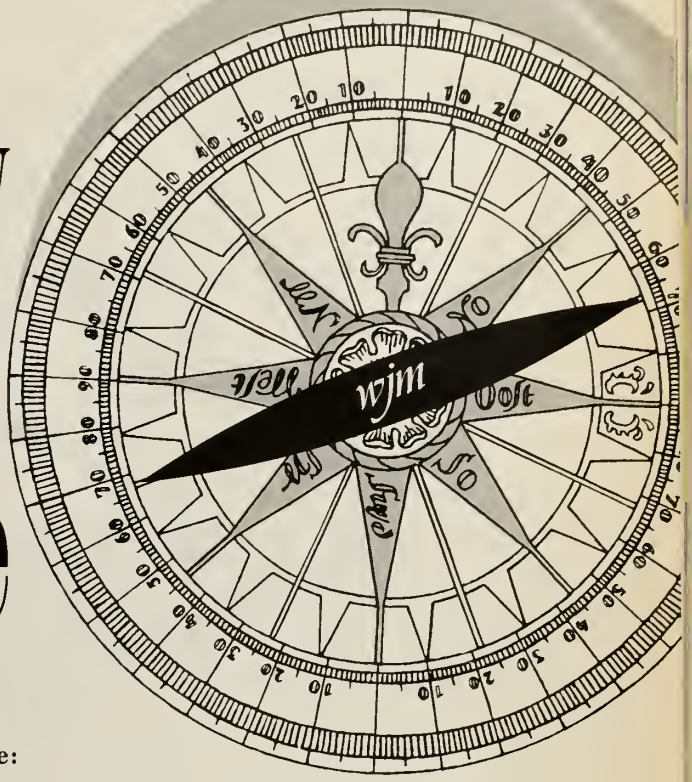

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(Continued from Page 406)

January 19-21—**Duplex Imaging.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sat. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 21-22—**Workshop on Percutaneous Disectomy.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Sat-Sun. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 24-27—**MRI for Technologists—Symposium and Workshops.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Tues-Fri. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

February 23-25—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Rancho Mirage. Thurs-Sat. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

SURGERY

October 29-30—**1988 Regional Review Courses in Hand Surgery.** American Society for Surgery of the Hand at Los Angeles. Sat-Sun. 12 hrs. $200. Contact: ASSH, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

December 1-4—**Bone Grafting: Biology and Application for Maxillofacial Indications.** Plastic Surgery Research Foundation at Le Meridien Hotel Coronado Bay, San Diego. Thurs-Sun. 21 hrs. $350. Contact: PSRF, PO Box 33387, San Diego 92103. (619) 692-9115.

December 3—**Reider Laser YAG & Argon Laser/Brachytherapy Symposium.** Center for Health Education, Long Beach. Sat. 9 hrs. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

December 3—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

January 13-14—**11th Annual Postgraduate Course: What's New in General Surgery.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

March 9-11—**Knee Reconstruction Surgery: ACL Repair, Patella Alignment and Total Knee Replacement.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Thurs-Sat. 30 hrs. Contact: Bonny Mower, Conference Coordinator, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 15-17—**Perioperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. 16 hrs. $350. Contact: UCSF.

March 16-19—**Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director of Medical Education, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

OF INTEREST TO ALL PHYSICIANS

October 15—**Office Psychiatry and the Primary Care Physician.** UCLA at Century Plaza Hotel, Century City. Sat. 6 hrs. $35. Contact: UCLA.

October 15-18—**Infectious Diseases: Part I of II.** EPIC Expeditions at Napa Valley. Sun-Tues. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 19-22—**Infectious Diseases: Part II.** EPIC Expeditions at Sonoma Valley. Wed-Sun. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 20-22—**38th Annual Regional Postgraduate Institute.** The Cypress Foundation at Doubletree Hotel, Monterey. Thurs-Sat. 11 hrs. $176. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

October 20-22—**What the Clinician Should Know About the Treatment of Chemical Dependence: A Review and Update for Physicians.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at Los Angeles Airport Marriott. Thurs-Sat. 19 hrs. $350. Contact: Gail Jara, California Society. 3803 Broadway, Oakland 94611. (415) 428-9091.

October 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 25—**Sexual Addiction and Chemical Dependency: The Hidden Connection.** Institute for Addiction Studies at Health Education Center, Oakland. Sat. $55. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609. (415) 652-7000.

October 27-30—**Clinical Nutrition.** UCD at Sonoma Valley. Thurs-Sun. Contact: UCD.

October 31-November 3—**Primary Care Update.** Interstate Postgraduate Medical Association at Bally's Reno, Nevada. Mon-Thurs. 24 hrs. $185. Contact: Interstate Postgraduate Medical Association, PO Box 1109, Madison, WI 53701. (608) 257-6781.

October 31-November 3—**Intervention Workshop.** McDonald Center for Alcoholism and Drug Addiction Treatment at La Valencia Hotel, La Jolla. Mon-Thurs. 27 hrs. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

November 4-5—**UCD Multi-Specialty Update: Medical Advances of the 80's.** UCD at Sacramento. Fri-Sat. Contact: UCD.

November 5—**Time Out: A Tune Up for Staff and Counselors in Profit and Non-Profit Settings.** Institute for Addiction Studies at Health Education Center, Oakland. Sat. $55. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609-3081. (415) 428-4104.

November 6—**State of the Art in Medicine—1988.** UCLA at Sheraton Universal Hotel. Sun. 7 hrs. $100. Contact: UCLA.

November 10-13—**Sexual Literacy: What is it? What do we know? What do we need to know? Whose responsibility is it?** The Society for the Scientific Study of Sex at the Cathedral Hill Hotel, San Francisco. Thurs-Sun. Contact: Bernard Goldstein, San Francisco State University, Biology Dept., 1600 Holloway Ave., San Francisco, 94132. (415) 338-1548.

November 11-12—**Photodynamic Therapy: Concepts and Methods.** Western Institute for Laser Treatment at Santa Barbara. Fri-Sat. 12 hrs. $350. Contact: Western Institute for Laser Treatment, 5333 Hollister Ave, Ste 233, Santa Barbara 93111. (805) 964-8432.

December 1-2—**Occupational HIV Infection: Risks and Risk Reduction.** UCSF at Le Meridien Hotel, San Francisco. Thurs-Fri. $220. Contact: UCSF.

December 1-3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Hyatt Regency, San Francisco. Thurs-Sat. 19 hrs. Contact: American Back Society, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

December 2—**Clinical Research and Addiction Studies.** Institute for Addiction Studies at Health Education Center, Oakland. Fri. $100. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609-3081. (415) 428-4104.

December 9-10—**American Academy of Pain Medicine: 5th Annual Meeting.** American Academy of Pain Medicine at Emerald Hotel, Anaheim. Fri-Sat. Contact: Dr Jack Pinsky, AAPM. (714) 634-6805.

December 24-30—**Advances in Medicine.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sat-Fri. 15 hrs. $400. Contact: Joe Harrison, MD, PO Box 10185, Lahaina, Hawaii 96761. (808) 661-8032.

January 17-21—**Intensive Course in Geriatric Medicine.** UCLA Multi-Campus Division of Geriatric Medicine at Beverly Hilton, Beverly Hills. Tues-Sat. 34 hrs. $265. Contact: Susan Vivell, UCLA Multi-Campus Division of Geriatric Medicine, Dept 32-144 CHS, Los Angeles 90024-1686. (213) 825-8255.

January 19-22—**Health Science Response to Child Maltreatment: 1989.** Children's Hospital & Health Center at Omni Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 20-22—**Urology and Gynecology for Primary Care Physicians.** UCSD at Hyatt Islandia Hotel, San Diego. Fri-Sun. 13 hrs. Contact: Edith S. Bookstein, UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Princess Resort. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 412)

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January 20-22—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at La Jolla Marriott. Fri-Sun. 18 hrs. $225. Contact: Bonny A. Mower, Conference Coordinator, Department of Academic Affairs, 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

January 29-February 3—**Selected Topics in Family Practice.** Tropical Seminars at King Kamehameha Hotel, Kona, Hawaii. Sun-Fri. 20 hrs. Contact: Tropical Seminars, North Kitsap Medical Center, 20700 Bond Rd NE, Poulsbo, WA 98370-9099. (800) 441-4439.

February 10-12—**58th Midwinter Clinical Conference.** Research Study Club at Moseley-Salvatori Conference Center. Fri-Sun. Contact: Research Study Club, PO Box J, South Pasadena 91030.

February 17-19—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 25-March 4—**Update: Controversies in Emergency and Primary Care.** Scripps Memorial Hospital Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 3-5—**Asia Pacific Alzheimer's Disease Conference.** Pacific Islands Geriatric Education Center at Hilton Hawaiian Village, Honolulu, Hawaii. Fri-Sun. 21 hrs. $300. Contact: Katherine Kim, Pacific Islands Geriatric Education Center, 347 N Kuakini St, Honolulu, HI 96817. (808) 523-8461.

March 5-8—**Asia-Pacific Osteoporosis Conference.** Kuakini Osteoporosis Center at Hilton Hawaiian Village, Honolulu, HI. Sun-Wed. 25 hrs. $450. Contact: Shirley Kuma, KOC, 347 N Kuakini St, Honolulu, HI 96817. (808) 547-9578.

March 19-22—**Annual Meeting of the Society for Adolescent Medicine.** Society for Adolescent Medicine at San Francisco. Sun-Wed. Contact: Edie Moore, 10727 White Oak Ave, Ste 101, Granada Hills 91344. (818) 368-5996.

April 8—**Antibiotics: 1989 and Beyond.** Grossmont District Hospital at Kona Kai and Tennis Resort, San Diego. Sat. 8 hrs. Contact: Verda Belyeu, CME Office, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

May 19-20—**Medical Consequences of Alcohol and Other Drugs.** UCSD. Thurs-Fri. 9 hrs. $105. Contact: UCSD.

IDAHO

September 2-5—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. 12 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 18-21—**Epidemiologic & Methodologic Problems in Determining Nutritional Status of Older Persons.** Sheraton Old Town Hotel, Albuquerque. Tues-Fri. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 28-29—**New Mexico Medical Society Interim Meeting** and **Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Journal Center Pyramid Holiday Inn, Albuquerque. Fri-Sat. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 11-13—**Adolescent Medicine.** Hilton Inn, Las Cruces. Fri-Sun. Contact: Marilyn Stark, NM Chapter, American Academy of Pediatrics, 7605 Mountain NE, Albuquerque 87110. (505) 265-7431.

December 1-3—**American College of Physicians—New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

December 9-10—**Trauma Update '88.** Clarion Four Seasons Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 24-26—**17th Annual New Mexico Thoracic Society Lung Disease Conference.** Taos. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 217 Truman NE, Albuquerque 87108. (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

November 17-18—**Laser Surgery: Gastroenterology** (Sponsor: UUMC). Thurs-Fri. 11 hrs. Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

December 1-2—**Laser Surgery: Angioplasty** (Sponsor: UUMC). Thurs-Fri. 11 hrs. Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

January 6-8—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). Fri-Sun. 15 hrs. Snowbird. Contact: (801) 581-8664.

January 12-14—**Arthroscopic Surgery** (Sponsor: UUMC). Thurs-Sat. Phoenician Resort, Scottsdale, Arizona. Contact: (801) 581-7601.

January 14-21—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). One week. Aston Genesis Resort, Park City. Contact: (801) 581-8664.

February 5-10—**A Practical Approach to Modern Chest and Musculoskeletal Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird. Contact: (801) 581-7553.

February 7-10—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Red Lion Inn, Salt Lake City. Contact: (801) 581-8635.

(Continued on Page 417)

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These two trials[1,2] used the currently recommended dosing regimen of cimetidine (400 mg hs) and ranitidine (150 mg hs). A comparison of other dosing regimens has not been studied.

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This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.*

Warnings: *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.*

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions: *The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.*

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions: *The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.*

Supplied: Capsules containing 25 mg. hydrochlorothiazide and 50 mg. triamterene, in bottles of 1000 capsules; in Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

OCTOBER 1988, VOL. XLV, NO. 10

Minding Your Own Business

Marshall B. Block, M.D.

There are occasions in everyone's practice when comments can be made to colleagues, patients, or office staff regarding the conduct or activity of another physician. Many of us prefer to keep these thoughts to ourselves rather than spread needless gossip and add to an already overburdened public disenchantment with our profession. Lawyers complain that it is impossible to find physicians to testify against colleagues in the same community. Patients complain that the Board of Medical Examiners and the various grievance committees at local and state level don't adequately deal with professional misconduct. Legal action has been taken against physicians who have expressed their reservations in no uncertain terms against other physicians in arenas which are not protected by peer review, i.e., cocktail parties, doctor lounges, etc. A "catch-22" situation has developed whereby the "due process" necessary for handling various complaints against physicians has in effect, handcuffed the process and hindered speedy resolution to what appear to be obvious problems.

A recent story relayed by my father is illuminating. While standing in line to return some shirts at a local department store a man in front of him in line was asking the cashier to sell him two shirts which, the day before, had been on sale, but had now been marked up to their regular price. He wanted the sale price which was about two dollars less per shirt. The salesgirl politely told him that it was not possible to do that, stated the sale was for one day, and the current price reflected the usual cost of the shirt. The gentleman persisted in several different ways, cajoling her to give him the shirts at the sale price. Finally after 15 minutes of haggling, my father, who was next in line, stepped up to the gentleman and said "Mister, enough is enough, stop badgering this woman, either take the shirts at the marked price or don't! Why persist in this harangue"? The gentleman turned to my father, put up his fists and said "If you don't mind your own business, I'm going to punch you in the mouth." Please bear in mind that this exchange was taking place between two men who are at least 80 years old. My father turned to the man and without flinching said "This is the kind of behavior that is going to make you go to hell instead of heaven when you die." The man dropped his fists and the shirts and quickly walked away. A few moments later when my mother, who was shopping at another part of the store, met my father, she noticed that he was very agitated and asked what had happened. He relayed the story to her and she responded "Why don't you mind your own business!" My father responded by saying "There was something inside of me that told me that what that man was doing was not right and I just couldn't keep quiet!"

Regardless of the legal restraints we all face, we must continue, much as my father did, to defend what is right and not back down. It's too easy to turn your back or look the other way. It's much harder to face the truth and deal with it in a constructive fashion. Not only does Arizona law demand it, more importantly our patients are dependent on us to do what is right.

Marshall B. Block, M.D.
Editor

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- Consolidation Benefits
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- Letter to the Editor
- Classifieds

New Legislation Is Not the Answer For the Uninsured 'Problem'

There are some 37 million non-elderly people in the United States who do not have health insurance. According to some people, this is a problem that must be dealt with through new legislation.

Before even considering legislation, policymakers should ask whether the 37 million citizens – 16 percent of the population – without health insurance necessarily constitute a problem. Who are the uninsured? Why are they uninsured? What are their income levels? Does lack of health insurance coverage limit or prohibit the uninsured population's access to needed health care?

Contrary to the typical assumption, in 1985 close to two-thirds of the uninsured, about 20.4 million, had incomes well above the poverty line. Furthermore, 8.8 million lived in families with incomes that were twice to almost four times the poverty level. Another 4.3 million lived in families with incomes of four times or more than the poverty level. This implies that many people who easily can afford health insurance simply are choosing not to buy it, or are refusing employer-provided plans. Two questions arise: Why might this be the case and should it be considered a problem?

In many respects, health insurance is similar to other forms of insurance. People who do not feel at high risk of losing their belongings to floods or earthquakes, for example, are unlikely to buy insurance against these hazards. Many people without health insurance can be viewed in this light. According to a study by Frank Sloan of Vanderbilt University and Patricia Danson of the University of Pennsylvania, almost 90 percent of the uninsured rate their health as good or excellent. From the 1985 data we learn that 52 percent of uninsured workers are 30 years old or younger – understandably an age group where health insurance might not be a priority. Even for a healthy person, health insurance premiums can be more than $1,000 a year. This is primarily to insure against the risk of becoming seriously ill –a small risk for people under 30.

The average insurance premium, plus deductible and co-insurance, will add up to far more spent each year on health care than a healthy person would otherwise spend on basic health services. So it makes sense for many people to spend their incomes on other things – better housing, food and clothing – rather than on health insurance they may never use. In addition, medical care costs that otherwise healthy people may be at higher risk of incurring, for example, those associated with accidents or employment-related injuries, often are covered by other types of insurance, including auto insurance and workmen's compensation.

Our analysis suggests that there are at least two important points being ignored. First, many people who can afford health insurance are simply choosing not to buy it. Why this should be considered a problem in a free society is not clear. Secondly, the majority of those without health insurance are in the age group that is least likely to experience serious medical problems. Again, this should hardly be elevated to the status of a "national crisis."

There are other uninsured people, of course. As of 1985, 11.2 million of the uninsured did not work, lived at or below the poverty line, and were not eligible for Medicaid. But mandating health insurance in the work place or creating a universal national health insurance program are not appropriate solutions. Such proposals would compound the problem by significantly in-

Continued on Page 6

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Clinical Competence

"Clinical Competence" is a term used often throughout the medical profession, but perhaps no where with more frequency than within our Colleges of Medicine. Clinical competence is what we expect of graduating medical students, housestaff completing training, physicians applying for licensure or board certifications, and practicing physicians on a daily basis in all of their patient and collegial contacts.

Despite the all-pervasive nature of this desired goal in clinical practice and despite our each probably being able to provide some sort of definition for the term, there is no one source work we can turn to which will satisfy us all. No one definition provided by the many specialty and subspecialty boards for their own disciplines encompasses all those things that might be subsumed by a definition for all specialties. Surveys have been conducted among practicing physicians, between different college faculties, and within the faculty of individual colleges of medicine. No one definition heretofore promulgated will satisfy all.

The University of Arizona College of Medicine has long accepted the premise that clinical competence is at least a two-pronged entity: Any student or physician, to be competent, needs both knowledge and skills requisite to the practice of medicine. We have accepted that the exact body of knowledge and the exact array of skills necessary to define competence is much more difficult to agree upon. But the basis of education at our College is clearly that glaring deficiencies in knowledge, in interpersonal skills, in skills requiring manual dexterity, in skills of reasoning and assessment, in skills of self-education, or in skills of personal growth and development can potentially lead to a state of incompetence. Further, incompetence will be identified by patients and/or colleagues when the care provided by any physician is not seen to be of the highest quality possible, the highest quality our patients deserve.

When we see incompetence in a colleague or when one of our patients adjudge us to be incompetent that assessment is usually based on a "gestalt" evaluation--an overall feeling that things could or should be better. That, too, is the way we in clinical medical education have for all too long assessed our students' abilities: The attending physician eyeballs a student's performance and writes a summary statement or fills out some checklist form that gives Honors, Pass, or Fail to a student without a careful attempt to tease out the strengths and deficiencies we each clearly have. If competence is to have a multi-pronged definition it should have a multi-pronged evaluation so that areas of weakness may be remediated, so that, thereby, our level of competence may increase. For the past twelve years at this College of Medicine we have continuously evaluated and assessed our students' clinical skills of patient interaction using Patient Instructors--lay members of the community who have actual diseases and who collectively submit to well over a thousand physical examinations or interviews each year. We believe that, through this program we have increased our students' awareness of the importance of these basic skills and have fostered a higher level of clinical competence among our young colleagues as they enter practice.

Only now are we beginning a similar sort of program in which we will embark upon a major underscoring of the importance of higher level clinical skills: differential diagnosis formulation, patient counseling and education, assessment of patient data, etc. This program, too, will depend heavily on real patient clinical material and a new cadre of specialized Patient Instructors who can present the same story, the same physical findings, the same patient reactions to each student being evaluated.

This program (based upon the work of Harden and Hart outside the United States as well as that of Barrows, Stillman, Petrusa and their respective coworkers in this country) is seen to be a more objective (than the current "gestalt" evaluations), more structured (than traditional oral examinations) mode of performing clinical evaluation. We hope that, by assessing multiple components of that overall nebulous "clinical competence" we will both be able to define these components more clearly and be saying to our students that these skills are all skills they must possess to provide high quality patient care.

For much too long we have relied on objective, written board examinations to certify a physician's knowledge base and inferred from that that he or she was competent to care for patients. What for us is an extremely exciting era in medical education is now beginning in Arizona--one in which we will be emphasizing even more than in the past the importance of skills attainment and the absolute necessity of perfecting those skills in order to deliver patient care. ❑

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Universal Problem, (Continued from page 2)

creasing labor costs and slowing job creation. As it turns out, only three million of the 37 million uninsured are working-poor or near-poor. Rather than securing health insurance coverage for these people, recent proposals could force their employers to eliminate many of their jobs or at least reduce them to part-time jobs. In countries that have nationalized health insurance, the problems are well-documented. Long queues for needed operations and the denial of life-sustaining treatments to the elderly are common methods of rationing services that can't be made "free" just because the government passes a law.

If the goal of public health care policy is to encourage more widespread health insurance coverage, there are sound alternatives for accomplishing this end. These include extending the tax deduction for health insurance premiums to the self-employed and to unincorporated business, and offering tax credits or deductions to all those who pay for health insurance out of their own pockets. In addition, federal and state regulation of employer health plans -- regulations that create barriers to setting up insurance plans -- should be repealed. These approaches would impose no extra burdens on the economy and would affirm the right of employers and employees to freely negotiate mutually beneficial compensation packages.

One thing is certain in making public policy: Misunderstanding an issue and ignoring the costs of the purported solution is a recipe for damaging legislation. The current effort to save the 37 million uninsured from what in large part are their own choices is not an exception. If any of these proposals eventually are enacted, economic growth will be stifled, unemployment will swell, many full-time jobs will be reduced to part-time positions, and increased consumer demand will lead to higher insurance premiums and health care costs. All of this will occur in the name of solving a problem that has yet to be clearly defined. ❑

Roy Cordato and Lauren Cook

Roy Cordato is an economist for a Washington, D.C., research organization and a fellow of The Institute for Humane Studies at George Mason University, Fairfax, Va. Lauren Cook is an analyst for the same research organization.

(Reprinted courtesy of The Business Journal, August 22, 1988)

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Consolidation Benefits

By
John Bull, M.D. Executive Director -- Medical Staff
St. Joseph's Hospital and Medical Center
and
Merlin Kampfer, M.D., Vice President for Medical Affairs
St. Luke's Medical Center

Over a year ago, a decision was made to embark on a phased consolidation of services which could eventually merge St. Joseph's Hospital and Medical Center and St. Luke's Health System. Already, great progress has been made as the two organizations work closely together to build a strong, viable relationship.

When consolidated, St.Luke's and St. Joseph's will create the second largest health delivery service in Arizona with over 1200 acute and behavioral health beds and some 250 long-term care beds. The new system will present to the community a broad base of specialized services including Barrow Neurological Institute, the Prentice Eye Institute, the Harrington Arthritis Research Center, advanced cardiopulmonary and neonatal programs, and a comprehensive mental and behavioral health network.

For physicians, a combined system would hold many advantages.

"When the consolidation is completed, physicians will be able to form an alliance to more adequately meet competition in the future," said Terry Ashoff Johnson, vice president of marketing for St. Joseph's and St. Luke's. "This is particularly crucial as the market moves toward more managed care contracts."

"Challenges presented by third party payors and health care regulators will be well served by the new system," noted John J. Buckley, Jr., President for St. Joseph's. "Not only will quality be enhanced, but cost effectiveness of the clinical, behavioral and research needs of the patient will be well served."

A primary concern for both organizations is to accommodate the needs of physicians who participate in managed care contracts, while at the same time continue to be responsive to those physicians who admit private pay patients.

"Initially, one of the reasons St. Joseph's was interested in the consolidation was a 'build or buy' decision. We needed bed space, and that meant raising capital for a new patient service tower or looking to outside resources already in existence," Buckley said. "Now that the Phoenix market is experiencing a temporary decline in patient census, that need is not as paramount.

"But we have to keep an eye to the future," he continued. "As we begin new services, sign new contracts and combine programs, we want to be able to maintain our current level of care and commitment. The consolidation positions us to be able to provide health care that is dictated by the needs of the community and by the physicians on our medical staffs."

In a 1987 survey conducted by *Medical Economics* magazine, physicians noted "greater ease of practice" as their primary practice goal aside from good patient care.

Johnson noted that the consolidation would greatly enhance "ease of practice" for physicians.

"For example, physicians would have increased flexibility in scheduling procedures," Johnson said. "Our desire is that he or she could make one phone call and find out the availability at all system facilities simultaneously, instead of phoning each one separately."

Bonnie Meyers, consolidation coordinator for St. Joseph's and St. Luke's, noted that a major advantage to physicians would be a broadened patient referral base.

"Specialists would be able to draw upon increased number of primary care physicians," Meyers said. "Likewise, primary care physicians would have more

specialists to whom they could refer their patients. Physicians would also have a wider geographic area from which to draw upon referrals, since our facilities stretch from central Phoenix to the east valley."

Currently, St. Joseph's and St. Luke's are investigating the consolidation of certain clinical services that fall under the service lines of both institutions.

"We are carefully evaluating the programs and services of both St. Joseph's and St. Luke's," Buckley said. "There are some we have in common and others that are unique. Where it makes sense to do so, we will consolidate services and facilities. Where it makes more sense to stay apart and maintain separate identities, we will be doing that."

Already, the management contract has helped St. Joseph's and St. Luke's achieve certain economies of scale, particularly in administrative areas such as marketing, personnel and communications. More importantly, the consolidation has resulted in improved patient care.

A recent example is the management agreement between the Women's Care Center of St. Joseph's and Tempe St. Luke's Hospital. St. Joseph's provides Tempe with a full-time nursing manager and a part-time medical director for its obstetrics/gynecology program.

"Throughout the challenging and tedious process of the consolidation, physicians have continued to play key roles, maintaining an active voice and high visibility," Buckley said. "Representatives from the medical staffs serve on each board of directors, on the consolidation coordinating committee, and are assisting administrators in the evaluation of clinical programs and services. The new system represents, for all involved, an opportunity to shape future health care practices in Phoenix and in Arizona."

On April 25, 1988, St Luke's Health System welcomed aboard Bill Murray as the newly appointed president. Murray comes to St. Like's from St. Vincent Hospital and Medical Center in Billings, Montana where he served as president and chief executive officer.

"I've been very impressed with St. Luke's broad-based community support, strong volunteer base and the commitment of its physicians," Murray said. "I'm excited about the opportunities which exist for St. Luke's, particularly as it moves forward to consolidate with St. Joseph's. I believe the blending of these two organizational cultures will have a synergistic effect."

Original negotiations between the two systems began in late 1986. In April 1987, a letter of intent and management contract were signed by the two boards, becoming effective on May 14. A continuation of these agreements, contingent upon St. Luke's ability to reduce its debt, were signed by St. Joseph's and its parent company Catholic Healthcare West in August, 1987. Approval came from the board of St. Luke's Health System in September.

On December 18, 1987, a plan to consolidate and an enhanced management contract were signed by the governing boards of both systems and by CHW.

Buckley pointed out that a major reason for the consolidation's success to date has been a shared commitment by both St. Joseph's and St. Luke's to helping patients.

"Both organizations are built on faith-based traditions, St. Joseph's being Catholic-sponsored and St. Luke's being Episcopal-sponsored," he said. "The goal of the combined system is to enhance the quality of human life by providing services that prevent illness, restore and improve health, alleviate suffering, and care for the dying in an environment which fosters dignity and respect for each individual. The consolidation of these two systems will continue to strengthen the mission and philosophy of the Sisters of Mercy to service those in need."■

"Both organizations are built on faith-based traditions, St. Joseph's being Catholic-sponsored and St. Luke's being Episcopal-sponsored,"

Guest Editorial

One of the strengths of the "American way" lies in our freedom to offer a plurality of solutions to problems. Social injustices can be scrutinized from many viewpoints: therefore, we have the capacity for flexibility -- for refining solutions, changing procedures economizing both in effort and investment, while continually searching for better ways to resolve our social dilemmas.

Let me summarize a case which, in my opinion, glaringly reveals the failure of one particular social measure and substantiates a demand for improvement or refinement.

Her name was not Susie so I shall call her that. Susie was a lady approaching her middle years, the mother of two teenage children, who had had several years of a happy marriage who, when I met her, held a Master's degree in Education, and had been an exemplary kindergarten teacher for many years; but her inordinate dependency on beer eventually interfered with good judgement and productivity and she was terminated. I met her on the day that she contested the School Board's action: she in a hospital bed, diagnosed a chronic substance abuser and one with significant dementia largely affecting the areas of her judgement and appreciation of higher values. Would that such a diagnosis had been respected some years earlier!

At that time, due to the interest and dedication of her generalist, she eventually came to the attention of the local Alcohol Reception Center and it was seen fit to commit her for alcoholic treatment in a Phoenix facility, which commitment was terminated by her mandatory discharge in ninety days. Unfortunately, she was sufficiently impaired in judgement and her addiction so strong that her sobriety was not maintained. Three months after leaving the Phoenix facility she was brought to one of our Tucson hospitals, unconscious from having struck her head while suffering a seizure. In the ER she had a respiratory arrest and was admitted to the ICU where she was treated for aspiration pneumonia. After her transfer to the ward I entered the picture, having been called to be a consultant. A previously determined cerebral atrophy was confirmed, again, by CAT scan; and Susie, as she recovered, continued to show evidence of confusion which only very slowly cleared, and her ability to sustain attention and utilize good judgement remained severely impaired. When her discharge was imminent, attempts were made to find a place for her. She was refused commitment through the local Alcoholic Reception Center because she had already failed that route. An attempt was made to have her committed and incarcerated eventually in the State Hospital; but, since her qualifying dementia was the direct result of alcohol, she was, by definition according to some bureaucratic law, disqualified as not being a mentally incapacitated person. Repeated pleas to have her recognized as an incapacitated person not only because of her affinity for alcohol but also incapacitated because of her dementia, fell on deaf bureaucratic ears. (Perhaps, too, it is not unlikely that the fact she was of modest means and her elderly parents lived on a fixed income quelled the interest of those involved in providing long-term care in a controlled and therapeutic environment.) Eventually, Susie was granted hospital freedom, then passes, and finally, in desperation and lacking any alternative, she was discharged to her own care but to reside with her elderly and apprehensive parents. I lost track of her for a brief time, then her mother came to me seeking advice regarding a possible management of her daughter. This, of course, proved to be a heart-wrenching exercise in futility for both of us as we searched for some mode of guaranteeing the sobriety and safety of one as demented as Susie, intent on alcoholic oblivion and self-destruction.

Earlier this year I received the final note in this saga. Susie's mother had been hospitalized for a few days in December, during which time there had been a rare day of snowfall in Tucson. When she came home, Susie was gone; but there had been previous episodes of this sort, so she said a prayer that her daughter would be looked after and protected. When the snow melted, Susie's lifeless body was found in the garden.

So ends the tragic story of a lady of talent and proven social worth who chose to destroy herself; and we, although we know better, and despite our ethical considerations, we permitted her to do this. Her civil liberties were preserved; she was allowed to do this... to destroy herself. By a bureaucratic definition she was barred from effective treatment and protection when she needed it most. I do not feel that her demise is an indictment of our medical system; but it is certainly a sad commentary on our sense of social responsibility. There has got to be a better way! ■

Hubert E. Wuesthoff, M.D.

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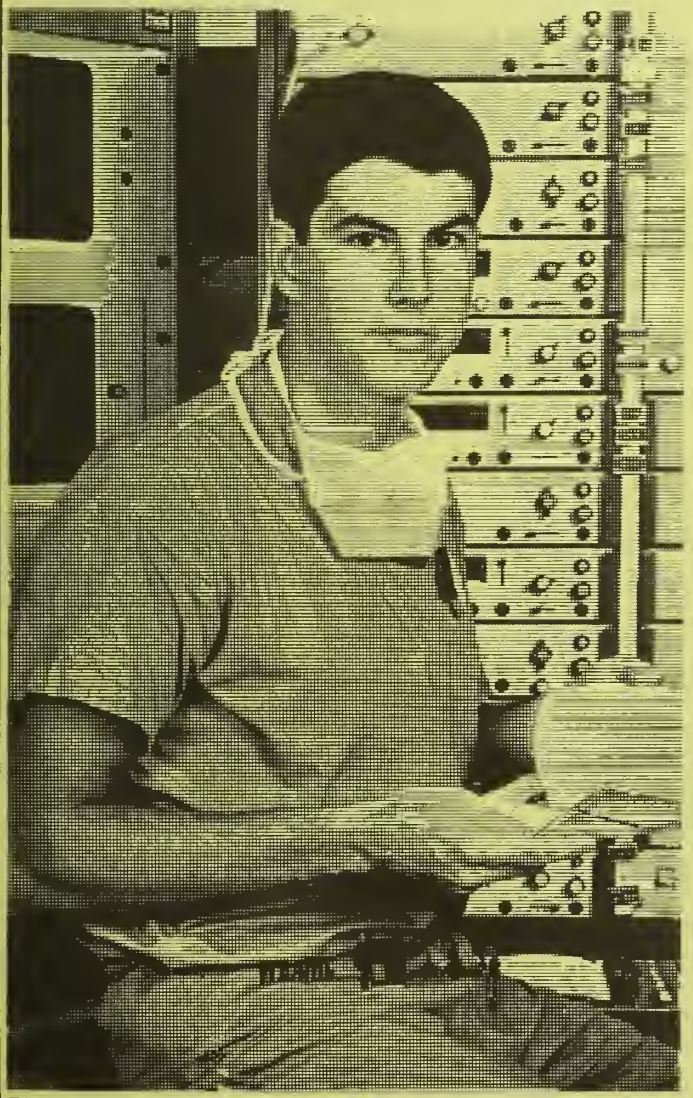

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General Surgery
4151 North 32nd Street,
Phoenix
Tufts University School
of Medicine - 1966
Kent J. Lyon, M.D.
Endocrinology,
Internal Medicine
9220 East Mountain View Road
Scottsdale
University of California at Los
Angeles School of Medicine - 1978
Medo Mirza, M.D.
Pediatric Surgery
2204 South Dobson Road
Suite 203, Mesa
Medical Faculty of Freien
University, Berlin - 1964
Douglas W. Ragland, M.D.
Family Practice, Legal Medicine
4425 West Olive Avenue
Glendale
University of Iowa
College of Medicine - 1972
Clive H. Sell, M.D.
Ophthalmology
525 North 18th Street
Suite 501, Phoenix
Vanderbilt University School
of Medicine, Nashville - 1980
Kathryn R. Slaine, M.D.
Pediatrics
2302 North 75th Avenue
Phoenix
University of Texas School of
Medicine, Galveston - 1982
J. Clarke Stevens, M.D.
Neurology
13400 East Shea Boulevard
Scottsdale
University of Alberta
Faculty of Medicine - 1965

PIMA

Wayne O. Alani, M.D.
Orthopedic Surgery
1779 West St. Mary's Road
Tucson
University of Texas Medical
School, San Antonio - 1983
Richard R. Boyle, Jr., M.D.
Diagnostic Radiology
3170 East Ft. Lowell
Tucson
University of Utah
College of Medicine - 1982
Steven I. Rosenfeld, M.D.
Obstetrics & Gynecology
839 W. Congress Street
Tucson
New York Medical School - 1984
Sam E. Sato, M.D.
Ophthalmology
Pediatric Ophthalmology
6535 East Carondelet Drive
Suite 310, Tucson
Case Western Reserve University
School of Medicine - 1979
Richard A. Smock, M.D.
Internal Medicine
630 East Alvernon Way
Tucson
University of Pennsylvania
School of Medicine - 1977
Linda S. Turner, M.D.
Obstetrics & Gynecology
2330 North Rosemont Boulevard
Suite B, Tucson
University of Arizona
College of Medicine - 1978
Mark T. Yoshino, M.D.
Radiology
3170 East Ft. Lowell Road
Tucson
University of Southern California
School of Medicine - 1981

RESIDENT

MARICOPA

Thomas J. Brown, M.D.
Neurology
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Phoenix
University of Oklahoma
College of Medicine - 1987
Patricia R. Reiff, M.D.
Family Practice
1300 North 12th Street
Suite 605 - Phoenix
University of Texas Southwestern
Medical School, Dallas - 1986
Neal J. Clinger, M.D.
Diagnostic Radiology
Arizona Health Sciences Center
Radiology 1535, Tucson
University of Washington
School of Medicine - 1984

STUDENT

PIMA

Michael Bulola
1201 East Drachman
Suite 216, Tucson
University of Arizona
College of Medicine - (1989)
Ld R. Herzog
449 East Elm, Tucson
University of Arizona
College of Medicine
Gregory L. Peare
1201 East Drachman
Suite 216, Tucson
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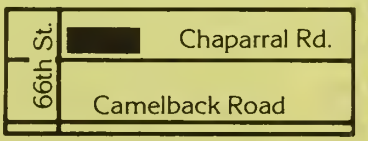

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Through a statewide program administered by the Arizona Council for the Hearing Impaired, special communication devices are distributed to the state's deaf, deaf-blind, speech impaired and severely hearing impaired residents. The TDD (Telecommunication Device for the Deaf) is a keyboard unit that allows the user to type their messages when connected to the telephone. The person at the other end of the telephone line must also have a compatible device. Both parties communicate by typing their messages back and forth.

The TDD has been around for some twenty years, however, new technology has converted it into a small lightweight battery unit that allows the user to make calls even from pay phones. Cost has been the major problem for most potential users, until the state of Arizona began providing them to certified residents on a loaned basis.

Individuals who cannot use the telephone because of their hearing loss or speech problems complete an application form which requires certification by either an audiologist, speech pathologist, person authorized to practice medicine in Arizona or some hearing aid dispensers. Once approved by the Council for the Hearing Impaired, the applicant is scheduled for a two-hour training class on how to use the unit.

Historically, the deaf who had such a machine, were only communicating on the telephone with other deaf or TDD users. The state has devised a relay system that allows the TDD user to call anyone in the world! Sound familiar? The hearing community has had that access for decades.

The Arizona Relay Service is housed in Phoenix and operates

twenty-four hours a day, seven days a week. The TDD user calls the relay center and tells (types) the relay operator the telephone number they wish to call. The relay operator then using another telephone line calls the non TDD user. Once on the line, the relay operator reads the TDD message to the non TDD user and types this message to the deaf TDD user. This unique service is offered to the community at no cost to the user, be he deaf or hearing. At present the relay center handles 21,000 calls a month, and is increasing at a rate of 1.7% per week.

The deaf and other TDD users are now able to call anyone in the world, that is if they identify how they want to pay for long distance charges. The TDD and the Relay Service have become the deaf man's ramp to the world's telecommunication system.

Since the calls into the relay center often result in the caller having to hold, many TDD users are hoping to see private businesses and hospitals obtain a TDD. Hospitals are taking a second look at how they can accommodate the hearing impaired. One way to assist communication is to have amplified hand sets available for the in-house patient. A spare TDD for patient usage is also advisable. Being able to call home during a stay in the hospital can make recovery a more pleasant and speedy process.

Closed captioned television decoders are also nice to have for patients. These machines allow the television viewer to read the words on the TV screen instead of trying to blast everyone else out of the room with the highest volume setting.

The name of the game is to communicate, and the speech and hearing impaired are doing their best to communicate with you. Perhaps your hospital needs to review how they are communicating with those patients who happen to have a hearing loss. Sign language interpreters play a key role in communications desired between the physician or hospital staff and the deaf patient.

If you want more information about TDDs, closed captioned television decoders, or sign language interpreters, then you need to contact the *ARIZONA COUNCIL FOR THE HEARING IMPAIRED (a state agency), 1300 West Washington, Phoenix, AZ 85007. Telephone - 255-3323 or toll free in Arizona only -- 1-800-352-8161.*

Stuart R. Brackney
Director, Council for the Hearing Impaired

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LETTER TO THE EDITOR

All of us are well aware of problems in continuing medical education. On many occasions the presenters are researchers whose information is of limited clinical value. Alternatively, the speakers although well-educated in practical aspects of medical care, lack the skills to communicate the information. Furthermore, didactic lectures tend to become tedious and the audience, with time, loses interest. It is for these reasons that the Southwest Allergy Forum was started several years ago to help practitioners in the field of allergy better understand evolving facets of their practice. The "Southwest Allergy Forum, 1989" should provide those interested in allergy and related diseases an opportunity to learn in a manner usually not available in other conferences. The conference to be held at the Registry Resort in Scottsdale on April 6th through 9th, 1989, will enable participants to have the opportunity to examine current developments in selected fields of Allergy-Immunology and to integrate the most current information as it relates to the allergy patient. Discussion by the presenters of specific questions the audience has will be given high preference in structuring of the meeting. It is hoped that by a greater intertake between the presenters and the audience that the problems enumerated above will be avoided. Previous conferences have been successful in this regard and therefore it is hoped that the forthcoming meeting will be of value to all practitioners in this field. The Baylor College of Medicine Office of Continuing Medical Education is sponsoring the meeting which will allow Category I credit for the Physicians Recognition Award of the American Medical Association to be given to those physicians attending. ❑

Merle S. Scherr, M.D.
Scottsdale Medical Pavilion, Suite 350
7331 East Osborn Drive
Scottsdale, AZ 85251

Medicare Revises Patient Liability Limits

Changes are forthcoming regarding Medicare's limitation of liability provision applicable to assigned and nonassigned claims.

The basic purpose of the limitation of liability provision is to protect beneficiaries from liability in Medicare denial cases under certain conditions when services they received are found to be excluded from coverage as not reasonable and necessary.

Where items or services are denied because they are determined to be not reasonable and necessary, the Medicare program makes payment when neither the beneficiary nor the physician or supplier knew, and could not reasonably be expected to have known, that the items or services were excluded.

When the beneficiary did not have such knowledge, but the physician or supplier knew, or could have been expected to know, of the exclusion of the items or services, the liability for the charges for the denied items or services rests with the physician or supplier. When the beneficiary knew or could have been expected to know that the items or services were excluded, the liability for the charges rests with the beneficiary.

The following statement will satisfy the requirements of the physician's/supplier's advance notice and the beneficiary's agreement to pay.

Physician Notice:

"Medicare will only pay for services that it determines to be 'reasonable and necessary' under section 8162(a)(1) of the Medicare law. If Medicare determines that a particular service, although it would otherwise be covered, is 'not reasonable and necessary' under Medicare program standards, Medicare will deny payment for that service. I believe that, in your case, Medicare is likely to deny payment for (specify particular service(s)) for the following reasons: (the physician gives the reason(s) for his or her belief."

Beneficiary Agreement:

"I have been notified by my physician that he or she believes that, in my case, Medicare is likely to deny payment for the services identified above, personally responsible for payment.

Signed,"

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To be acceptable, the advance notice must give the beneficiary an idea of why the physician is predicting the likelihood of Medicare denial so that the beneficiary can make an informed decision whether or not to receive the service and pay for it out-of-pocket.

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Further information concerning this will be in the "Special Edition Dear Doctor/Supplier" letter, which will be released sometime in September. These changes will be effective for claims processed on or after September September 1, 1988.

AMA Sets Program For Impaired Health Professionals Conference

The American Medical Association's ninth National Conference on Impaired Health Professionals will be held October 26-30, at the Chicago Marriott Hotel.

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Featured speaker at the closing session Sunday will be Stephen Allen, Jr., M.D., son of comedian Steve Allen, who will speak on the topic of "Medicine in the 80s: If I Didn't Laugh, I'd Cry." Allen is a Board Certified Family Physician who combines wit and entertainment in emphasizing the value of laughter and play in handling stress today.

In addition to information sessions, the program will offer research presentations, poster sessions, exhibits and a media mart.

A special research symposium on drug abuse will precede the impairment program on Wednesday, October 26, from 1 - 4 p.m. at the Marriott. Topics will range from substance abuse patterns of entering medical students and research on the treatment of drug abuse to the use of naltrexone in the treatment of opioid dependent health professionals and the genetic vulnerability to alcoholism.

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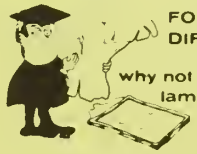

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Clinical Investigation

Symptoms and Routine Laboratory Abnormalities Associated With Coccidioidomycosis

MICHAEL L. YOZWIAK; LINDA L. LUNDERGAN, MD; STEVEN S. KERRICK, MD; *and* JOHN N. GALGIANI, MD, *Tucson*

To assess the relationships of various symptoms and other early findings to the diagnosis of primary coccidioidomycosis, we devised a 40-question survey that was completed by 556 college students seeking medical care for illness possibly due to Coccidioides immitis. *The results of routine laboratory studies on these patients were also compiled. Of 269 who had coccidioidal antibody determinations and other diagnostic tests, coccidioidomycosis was diagnosed in 36 (13%). By logistic regression procedures, an elevated erythrocyte sedimentation rate, male gender, "red lumps on shins," recent arrival to an endemic area, acuteness of symptoms, and decreased total peripheral blood lymphocyte counts were independent factors positively associated with infection (P<.05). Relative risk analysis indicated that 60% of patients with four or more of these factors were found to have coccidioidomycosis. Other significantly but not independently associated factors were an increased total leukocyte count, chest pain with breathing, fever, an absence of hoarseness, and an abnormal chest roentgenogram.*

(Yozwiak ML, Lundergan LL, Kerrick SS, et al: Symptoms and routine laboratory abnormalities associated with coccidioidomycosis. West J Med 1988 Oct; 149:419-421)

For college students in regions endemic for *Coccidioides immitis,* about 4 per 1,000 each year seek medical attention with symptoms related to coccidioidomycosis.[1] Numerous symptoms and other findings have been associated with infection, including fatigue, cough, abnormal roentgenogram of the chest, chest pain, rash, and male gender.[2] Little information exists, however, regarding the specificity of these or other associated findings. Thus, it is not known whether any are of value to assist in diagnosing coccidioidomycosis. In an attempt to elucidate this question, we embarked on a prospective study of patients' demographic factors, symptoms, and routine laboratory measurements in relationship to a subsequent diagnosis of coccidioidal infection. The results of this effort are the subject of the present report.

Patients and Methods

A questionnaire was developed by a consensus of physicians who were familiar with coccidioidomycosis. The survey contained 40 questions in the general content areas of demographics and pulmonary and nonpulmonary symptoms (a copy of the complete questionnaire is available on request from the corresponding author). The questionnaire was distributed from September 1984 to March 1986 to any student seen at the University of Arizona (Tucson) Student Health Service who would subsequently be skin tested for coccidioidomycosis. Most of these students ere otherwise healthy and had no knowledge or roentge raphic evidence of a previous coccidioidal infection.

Subsequent medical care was ided by one of eight physicians on the staff irrespectiv f participation in the survey; further evaluation for the possibility of coccidioidal infection was at the physician's discretion. If coccidioidal infection was considered possible, the evaluation included tests for coccidioidal antibodies,[3,4] skin testing with coccidioidal antigen,[5] a roentgenogram of the chest, and a complete blood count. Many patients with negative skin tests were retested within a month to determine if a change in skin test status had occurred. Other tests were repeated as deemed necessary.

As a result of these evaluations, patients were categorized into one of three groups: a diagnosis of recent coccidioidal infection could be established (case), a diagnosis of recent coccidioidal infection could not be established (noncase), or insufficient information was available to determine whether the patient had a coccidioidal infection (indeterminate). To be included as a case required at least one of the following criteria: detectable serum precipitating-type antibodies[3] or complement-fixing antibodies for coccidioidin[3,4] at a minimum of 1:2 serum dilutions, or cutaneous hypersensitivity to coccidioidin 1:100 (Iatric Corporation, Tempe, Ariz) only if a similar skin test were found to be nonreactive within the previous month. For the purposes of this analysis, noncases had at least one serologic study and neither of the two diagnostic criteria were met. The remaining patients were classified as indeterminate.

Data from the questionnaires and laboratory studies were entered into a data base (R:base 5000, Microrim, Inc, Bellevue, Wash) and analyzed using a statistical applications program (Systat, Systat Inc, Evanston, Ill).

The initial review consisted of examining the distributions of responses for each question and laboratory measure-

From the Medical and Research Services, Section of Infectious Disease, Veterans Administration Medical Center, and the Student Health Service, Department of Internal Medicine, University of Arizona College of Medicine, Tucson.

Reprint requests to John N. Galgiani, MD, Medical Service (111), VA Medical Center, Tucson, AZ 85723.

TABLE 1.—*Symptoms and Routine Laboratory Abnormalities Independently Associated With Coccidioidal Infection*

Variable	*P Value*	*Relative Risk*	*Risk*
Erythrocyte sedimentation rate	<.001	.247	>28 mm/hr
Gender	.007	.195	Male
"Red lumps on shins"	.004	.174	Present
Years residence in endemic area	.001	.160	<4 yr
Duration of symptoms	<.001	.128	<1 wk
Number of lymphocytes	.050	.091	<1,570/μl

ment in the entire sample. Continuous variables were then arbitrarily divided into ranges for further analysis. Relatedness of these groups to the diagnosis of coccidioidal infection was determined by Pearson's χ^2.[6] Factors that were determined significant ($P < .05$) were then analyzed by stepwise logistic regression procedures to determine their independence.[7] Independent variables were then used to construct a model for coccidioidal risk, P, through the following equation:

$$\ln (P/1 - P) = B_0 + B_1X_1 + B_2X_2 + \ldots + B_nX_n$$

where ln is the natural logarithm; $B_1, B_2, \ldots, B_n$ are regression coefficients estimated from the data in a stepwise procedure, and $X_1, X_2, \ldots, X_n$ are the individual factors being assessed. The degree to which any single factor correlates with other factors as predictors of disease is based on the coefficient value (B), with B_0 being the equation constant. Relative risk factors are based on a scale ranging from zero to one in which a value of one represents the highest risk of disease.

Results

During the 18-month period, our questionnaire was distributed to 556 patients. Of the 269 patients who received serologic evaluation and skin testing, coccidioidomycosis was diagnosed in 36 (13%). Of these, 26 were diagnosed serologically and in 10, skin tests converted from negative to positive within a month. The diagnosis was indeterminate for the remaining 287 patients.

A total of 40 questions and 6 routine laboratory results—including roentgenographic studies—produced responses for 11 that were significantly associated with cases of coccidioidal infection. These were erythrocyte sedimentation rate, male gender, "red lumps on shins," years of residence in an endemic region, acuteness of symptoms, number of peripheral blood lymphocytes, total peripheral blood leukocyte count, abnormal roentgenogram of the chest, chest pain with breathing, fever, and hoarse voice. When these factors were subjected to logistic regression procedures, six were identified as independent (Table 1). Erythrocyte sedimentation rate was found to have the greatest individual predictive power, with 53% of the infected population having a value of greater than 28 mm per minute. Men constituted 58% of cases even though they represented only 34% of the total population. The variable, "red lumps on shins," was only present in 20% of cases but its prevalence was even lower (5%) in noncases. The other three independent factors—length of residence within the endemic region, duration of symptoms, and total number of peripheral blood lymphocytes—were all inversely related to the likelihood of coccidioidal infection.

Several findings were common in both patients with coccidioidal infection and other patients as well so that their specific association with coccidioidal infection was not statistically significant. These included decreased energy level, headache, and fatigue, which occurred in 88%, 86%, and 81% of patients with coccidioidomycosis and in 85%, 69%, and 85% of noncases.

Relative risk distributions for patients with and without coccidioidal infections are shown in Figure 1. It can be seen from these histograms that the risk of disease among the negative case group (mean risk value = .21) closely resembles that of the group for whom infection was indeterminate (mean risk value = .25). In contrast, the distribution for cases (mean risk value = .52) was shifted toward the positive predictive end of the scale. Of the 25 patients who exhibited four (having a relative risk of 0.6 or greater) of the six predictors, 15 (60%) were diagnosed with coccidioidomycosis.

Discussion

This prospective study indicates that some symptoms and other early findings in patients seeking medical attention for respiratory complaints are significantly associated with coccidioidal infections. Because this study was done in predominantly healthy college students within an area endemic for coccidioidomycosis, the general relevance of these findings to other regions of the country or to other patient groups will necessarily require substantiation. Similarly, the instrument

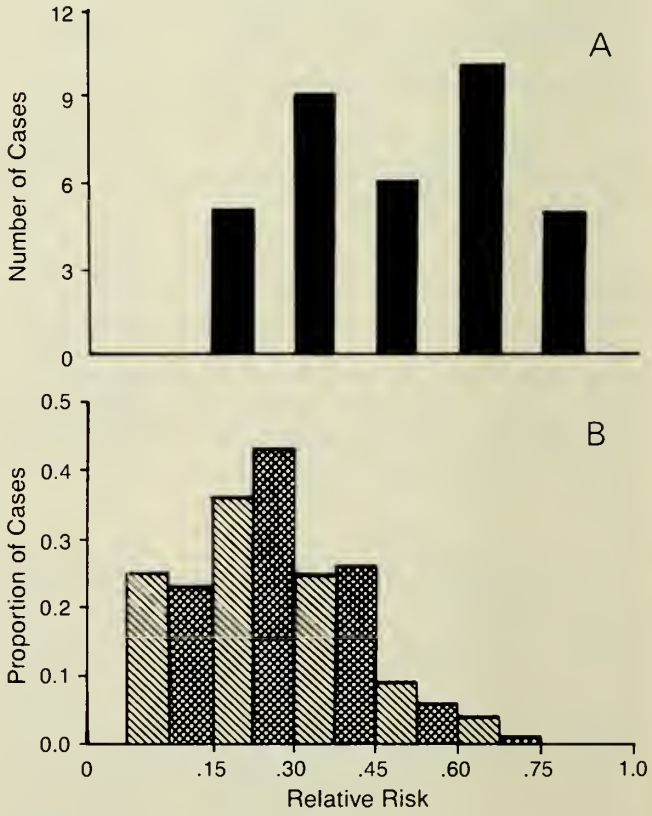

Figure 1.—The graphs show the distributions of the estimated likelihood of coccidioidal infection among 556 patients seeking medical attention for symptoms suggesting the possibility of coccidioidomycosis. The relative risk values are based on a standardized scale from 0 to 1 in which 1 represents the highest risk of disease. Panel A represents the relative risk distribution of 36 patients diagnosed with coccidioidomycosis. Panel B represents the relative risk distribution for those in whom the evaluation for coccidioidal infection was negative (hatched bars, n = 269) and for those in whom infection was indeterminate (crosshatched bars, n = 287).

that we devised was relatively arbitrary, and surveys seeking other information or using other methods may obtain results different from those reported here. Nevertheless, these findings indicate that at least under certain circumstances associations exist.

Some of these associations corroborate previous clinical impressions. As examples, fever, an abnormal roentgenogram of the chest, chest pain with breathing, having a skin rash (general), a recent arrival to an endemic region, an elevated erythrocyte sedimentation rate, and male gender were all found to be significantly more frequent in patients with coccidioidomycosis in our study. Other associations had not been previously noted, however. These included brevity of symptom duration before seeking medical attention, absence of a hoarse voice, and a decreased number of total peripheral blood lymphocytes. Several other complaints such as headache and fatigue, although found frequently in coccidioidal patients, were also frequent in patients in whom coccidioidal infection was not diagnosed and therefore did not discriminate among the groups. It is possible that our diagnostic methods may have missed some cases. Thus, with more sensitive methods, some additional symptoms might have been found to correlate with coccidioidal infection.

When subjected to logistic regression analysis, six variables emerged that appeared independent and could be used to estimate relative risk. Although the design of our study resulted in a large number of patients in whom the possibility of coccidioidal infection could not be satisfactorily assessed, the distribution of their relative risk was similar to that of noncases. This suggests that our model might have been substantiated even if the data were more complete. Despite the differences between cases and noncases, the separation was not sufficient to recommend this model's use as an isolated diagnostic tool. If other independent variables could be identified, however, the model's practical value might be improved. The current study suggests that additional efforts in this regard are warranted.

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Clinical Medicine

Intestinal Parasites in Southeast Asian Refugees Two Years After Immigration

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We collected stool specimens from 2,520 Southeast Asian refugees who had resided in the United States for an average of 2.1 years. More than half reported receiving prior treatment of parasites. At least one parasite was discovered in 32%, and multiple parasites were found in 8% of patients. Hookworm, Giardia, Strongyloides, *and* Hymenolepis nana *were most commonly found. In comparison to studies done at the time of immigration, all parasites had decreased in frequency, but* Giardia, *hookworm, and* H nana *remain common. Although initial screening efforts may have failed to identify substantial numbers of infected refugees, poor compliance with treatment may also explain the persistence of intestinal parasites in our patients. The continued presence of* Giardia *and* H nana, *especially among children, may be explained by person-to-person transmission or autoinfection.*

(Molina CD, Molina MM, Molina JM: Intestinal parasites in Southeast Asian refugees two years after immigration. West J Med 1988 Oct; 149:422-425)

About 800,000 Southeast Asian refugees have immigrated to the United States since 1975.[1] The first group of immigrants was, in general, well educated and from upper socioeconomic classes, while later immigrants were from more impoverished backgrounds.[2] Many of the immigrants before immigrating to this country were detained for a time in refugee camps that had poor sanitation and only rudimentary health screening.[3,4] All present special challenges to health care practitioners because of language barriers, cultural differences in perceptions of disease, and health problems not often encountered by physicians in the United States.

Guidelines were published suggesting that health screening of all Southeast Asian refugees upon entry into this country include an examination of stool specimens for intestinal parasites.[5,6] Several reports of the prevalence of intestinal parasites in these people on arrival in this country were also published.[7-9] To our knowledge, no large-scale follow-up study of intestinal parasites in these refugees has been done.

At the Pacific Family Practice Medical Clinic (Long Beach, Calif), we have had the opportunity to care for approximately 5,000 Southeast Asian refugees. Most of these patients came from Cambodia, while a small percentage were members of the Hmong group from Laos. Most of the patients were agricultural workers before immigrating to this country. All were eligible for Medicaid at the time of the study. This study was done to obtain an estimate of the prevalence of intestinal parasites in a population of Southeast Asian refugees who had resided in this country for about two years and had presumably been screened for intestinal parasites on entering the United States.

Patients and Methods

Stool specimens were collected from 2,520 Southeast Asian refugee patients seen for the first time in the Pacific Family Practice Medical Clinic over a 12-month period. The specimens were collected in plastic containers with 15 ml of a solution of sodium acetate 1.5%, glacial acetic acid 2%, formaldehyde 1.6%, and water (Trend Scientific Inc, St Paul). The stool specimens were examined at the Pacific Hospital of Long Beach by licensed medical laboratory technicians using both the concentration[10] and trichrome staining methods.[11] Although a previous study showed that the sensitivity of stool examination to detect intestinal parasites increases with the increasing number of stool specimens submitted from the same patient,[12] we chose to screen with only a single stool specimen to make our study more directly comparable to previously published reports of screening for intestinal parasites in this population that were based on examining a single specimen.

We interviewed a random sample of 299 of the patients who had positive stool specimens. A verbal history was elicited.*

Results

Stool specimens were obtained from 2,468 Cambodian and 52 Hmong refugees over a period of 12 consecutive months. We interviewed 299 patients with positive stool examinations to determine how long they had resided in the United States and whether they had been previously treated for intestinal parasites. This represents 11.9% of all patients

*Ngoun Chhin, Rany Khuon, and Ratha Or served as translators and assisted in the care of the patients.

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submitting stool specimens and 37% of patients with positive stools. The mean length of residence was 2.13 ± 0.07 years (mean ± standard error of the mean [SEM]). Of the patients interviewed, 54% gave a verbal history of previous therapy for intestinal parasites, but we were unable to determine for which parasites they were treated or which drugs were used in their therapy. The male to female ratio was 0.8 to 1.0. Most of our patients were young; 65% were younger than 20 years, and 88% were younger than 40.

The parasites most frequently found were hookworm, *Giardia lamblia, Hymenolepis nana,* and *Strongyloides stercoralis.* Nearly a third of the patients (32%) had at least one parasite, and infection with several parasites was found in 8% of patients (Table 1).

The frequency of certain parasites varied with the age of the patient. *G lamblia* and *H nana* were found more frequently in the 0- to 19-years age group, while hookworm was most frequent in patients 20 years of age or older (Table 2).

Of the 299 patients with positive stools that we interviewed, 117 had resided in this country for less than two years. Of this subgroup, 60% reported receiving previous therapy for intestinal parasites. In all, 48 patients had resided in this country for less than a year, and half of them reported previous treatment.

About half of the 182 patients who had resided in this country for two years or longer (51%) reported receiving previous treatment of intestinal parasites. There were 119 patients who had resided in this country for more than three years (40% of the total group interviewed). Table 3 shows the distribution of parasites in this group. When these data are compared with the overall data in Table 1, it can be seen that the four most commonly found parasites—hookworm, *G lamblia, H nana,* and *Strongyloides*—occurred with an even greater frequency in those patients residing here more than three years as compared with all patients submitting stool specimens. Of the subgroup of 119 patients, 60 were younger than 19 years. In this group of children, we identified 26 cases of *Giardia,* 21 cases of hookworm, 9 of *Strongyloides,* 14 of *H nana,* 4 of *Clonorchis,* and 1 case of *Entamoeba histolytica.*

Of the 299 patients interviewed, 147 had hookworm. The length of residence in the United States for this subgroup ranged from 4 months to 6 years with a mean of 2.8 ± 0.7 years (mean ± SEM). Of the patients with hookworm, 39% had resided in this country for more than two years. We found 12 women with hookworm who had been here for four years, four who had been here five years, and one who had resided in this country for six years. Of the patients with hookworm, 55% reported previous therapy for intestinal parasites.

All patients with positive stool specimens were treated appropriately following guidelines outlined elsewhere.[13] In those patients in whom stool specimens were examined after treatment, 58% were free of parasites. We are not sure why treatment was not more successful, but noncompliance may play a large role. For example, in one family of six that had resided in this country for six months, we identified various parasites, at least one in each family member. The patients received appropriate treatment. Examining stool specimens after treatment showed that not a single parasite had been eliminated from any member of the family, leading us to conclude that they had not taken the medication. They all reported receiving previous treatment of intestinal parasites, making us further suspect that they were noncompliant.

TABLE 1.—*Parasite Infection Rates by Ethnic Group in 2,520 Southeast Asian Refugees*

	Ethnic Group			
	Cambodian N=2,468,		Hmong N=52,	
Parasite	Number	Percent	Number	Percent
Giardia lamblia	274	11.1	6	11.5
Hookworm	367	14.9	1	2.0
Hymenolepis nana	128	5.2	3	5.8
Strongyloides stercoralis	108	4.4	1	2.0
Trichuris trichiura	50	2.0	1	2.0
Ascaris lumbricoides	26	1.1	1	2.0
Clonorchis sinensis	42	1.7	3	5.8
Entamoeba histolytica	12	0.5	1	2.0

Discussion

This study was done to determine the prevalence of intestinal parasites in our patient population. The patients we care for are mostly poor immigrants from rural Cambodia. Nearly all were detained in refugee camps in Thailand, often under crowded and unsanitary conditions.[3,4] The earliest refugees often received good medical care, but as more and more Cambodians fled, the medical resources were overwhelmed. At first it was thought that intestinal parasites were not a major problem in Southeast Asian refugees, probably attributable to the urban origins of the first refugees and reflecting the medical attention they received before immigrating.[5] The country of origin clearly affects the infection rate,[9,14] but the rate may be related more to the conditions in the refugee camps from which the various groups immigrated rather than to those of their native countries.

The studies of Parish[14] and Tittle and co-workers[15] show

TABLE 2.—*Parasite Infection Rates by Age in 2,520 Southeast Asian Refugees, Pacific Family Practice Medical Clinic*

	Age Group, yr							
	0 to 19, N=1,608,		20 to 39, N=578,		40 to 59, N=194,		60+, N=88,	
Parasite	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Giardia lamblia	247	15.4	26	4.5	7	3.6	0	0.0
Hookworm	128	8.0	172	29.8	49	25.3	19	21.6
Hymenolepis nana	102	6.3	23	4.0	6	3.1	0	0.0
Strongyloides stercoralis	55	3.4	38	6.6	12	6.2	3	3.4
Clonorchis sinensis	16	1.0	22	3.8	5	2.6	2	2.3
Trichuris trichiura	27	1.7	14	2.4	7	3.6	3	3.4
Ascaris lumbricoides	16	1.0	8	1.4	1	0.5	2	2.3
Entamoeba histolytica	6	0.4	4	0.7	3	1.5	0	0.0

TABLE 3.—*Prevalence of Intestinal Parasites in Refugees Residing in the United States for 3 Years or Longer*

Parasite	N=119 Number	Percent
Hookworm	58	49
Giardia lamblia	39	33
Strongyloides stercoralis	22	18
Hymenolepis nana	20	17
Clonorchis sinensis	10	8
Trichuris trichiura	6	5
Entamoeba histolytica	3	3
Ascaris lumbricoides	3	3

TABLE 4.—*Prevalence of Intestinal Parasites in Cambodian Refugee Children*

Parasite	This Study, N=1,608, %	Parish,[14] N=102, %	Tittle et al,[15] N=27, %
Giardia lamblia	15.2	23.5	22.2
Hookworm	8.0	27.4	59.3
Hymenolepis nana	6.3	10.8	11.0
Strongyloides stercoralis	3.4	14.7	37.0
Trichuris trichiura	1.6	2.0	7.4
Ascaris lumbricoides	1.0	2.0	11.1
Clonorchis sinensis	1.0	2.0	3.7
Entamoeba histolytica	0.4	2.0	7.4

that intestinal parasites were prevalent among Cambodian refugees upon arrival in this country. In Table 4 we compare our findings in patients residing for more than two years in this country with their results obtained from patients on arriving in this country. Their findings were striking enough to prompt the suggestion that even asymptomatic Southeast Asian refugee children be screened routinely.[14] This echoed the sentiment of Goldenring, who suggested screening all immigrant children who had resided in this country for less than three years.[16] In fact, several studies have shown significant numbers of Latin American refugees infected even beyond three years.[17,18] Although it can be argued that signs and symptoms should guide the use of laboratory studies, it has been shown that there is no correlation between symptoms and the finding of pathogenic intestinal parasites in Southeast Asian refugees.[19] Our data support Goldenring's assertion that parasites will continue to be found in immigrant children for as long as three years. They also show that intestinal parasites remain a problem in Southeast Asian refugees who have resided in this country for three years or more (Table 3), as suggested by Levin and Sarfaty.[20]

Most clinicians are familiar with the two most common pathogenic parasites encountered in our patients, hookworm and *G lamblia*, but many may be unfamiliar with the third most common parasite, *H nana*. More commonly known as the dwarf tapeworm, *H nana* is found throughout the world wherever crowded, unsanitary conditions exist. The parasites live for only a few weeks, primarily in the small intestine, but often they give rise to persistent infection due to autoinfection or reinfection by fecal-oral transmission. Manifestations range from no symptoms to anorexia, abdominal cramps, diarrhea, and even seizures.[21] Because of its potential as a pathogen and because simple, effective treatment is available, we have chosen to include it among our list of pathogenic intestinal parasites.

Although previous screening probably accounts for the reduction in frequency of all parasites (Table 4), the prevalence of *Giardia*, hookworm, *H nana*, and *Strongyloides* in our patients is unacceptably high. Furthermore, 65% of our patients are children or adolescents. The most commonly encountered parasites in our patient population have the potential to cause anemia and malabsorption, which may impair normal growth and development. Therefore, we think screening of asymptomatic Cambodian refugees is warranted. In addition to the obvious deleterious effects of infection with parasites in childhood, infection during pregnancy is another problem for our young families. Eradicating parasites before pregnancy might decrease the number of prenatal visits and the exposure of mother and fetus to harmful medications. Furthermore, certain parasites may be passed from the mother to the neonate.[22]

The reason for the continued high prevalence of intestinal parasites cannot easily be explained. Undoubtedly some patients escaped screening, others may have had falsely negative stool examinations at the time of immigration, and others (even though they reported previous treatment) may have been noncompliant with therapy. Many adult patients refuse to believe that they have intestinal parasites if they cannot "see the worms" in their stool. The finding that only 58% of patients were free of parasites after treatment and the anecdote previously mentioned in which an entire family showed no effect of treatment leads us to think compliance is often poor. Noncompliance with therapy may partly explain the persistence of intestinal parasites in these persons.

It has been our experience that considerable confusion exists about the life span of hookworm in humans. In experimentally produced hookworm infection in humans, Kendrick found hookworm eggs in the stool as long as six years after the initial infection,[23] and Palmer was still excreting eggs 15 years after infecting himself with hookworm.[24] Komiya and Yasuraoka in their authoritative review report the life span of hookworm in humans as being four to five years.[25] Hookworm is not indigenous to southern California, so our patients with hookworm must have acquired their infections in Southeast Asia. The finding of hookworm in patients residing in southern California for three to six years supports the notion that hookworm infection can persist in humans for years without reinfection.

Infection with intestinal parasites is a problem not confined to Southeast Asian refugees. Intestinal parasites are frequently found in immigrants from Latin America[17,18] and in migrant farm workers in this country.[26] As a growing proportion of the population of the United States comprises immigrants from Southeast Asia and Latin America, infection with intestinal parasites is likely to be an increasingly important health problem in this country.

Infection with intestinal parasites continues to be a problem among Southeast Asian refugees even after they have resided in this country for several years. A continued immigration of Cambodian and Hmong refugees from camps in Thailand can be expected for years to come. Western physicians must familiarize themselves with the special health problems that these new patients will present.

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Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

Principles of Extracorporeal Shock Wave Lithotripsy

Edited by Robert A. Riehle, Jr, MD, Assistant Professor of Surgery (Urology), Cornell University Medical College; Assistant Attending Surgeon, and Director, Lithotripsy Unit, The New York Hospital-Cornell Medical Center, New York, and Robert C. Newman, MD, Assistant Professor of Surgery, and Chief, Clinical Stone Service, Division of Urology, University of Florida College of Medicine, Gainsville, Florida. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 248 pages, $48.

This text represents a very good summation of the state of the art surrounding this new technique for the management of urinary tract calculi.

When one considers that the first application of this technique on humans was accomplished in the spring of 1980 by Christian Chaussy in Munich, followed by an extensive study of patients between that year and 1983, and that the first lithotripter was established in the US in March 1984, it seems remarkable that as of February 1986, 133 machines had been established worldwide, with 62 of those machines in the US having gone through Federal Drug Administration approval in the year 1984 following a six-site study in this country. This text represents an exceedingly fine progress report surrounding the four-year world experience since the major reports on clinical studies appeared in 1983.

The text spends considerable legitimate time reviewing the physics and geometry of extracorporeal shock wave lithotripsy, the biologic effects of shock waves, design considerations of a unit, all before patient selection and treatment are discussed. These sections are very worthwhile and give a good background of information to the practicing physician.

The sections of the book on patient selection and management do represent an up-to-date compilation of clinical data from several sources, which clarifies very nicely for the clinical urologist the learning curve that has progressed so quickly over the last few years with this technique.

I would recommend this text for its baseline information for the clinical urologist engaged in the care of people with renal stone disease.

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Intraluminal Thrombosis of Coronary Arteries in Fatal Myocardial Infarctions and in Failed Aortocoronary Saphenous Vein Grafts

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A review of autopsies of 648 patients who died of acute myocardial infarction showed the presence of intraluminal thrombi in 314 (48%). The left anterior descending coronary artery was principally involved in 172 cases, the left circumflex in 30, and the right coronary in 112. The length of survival after admission was identical for patients with thrombotic occlusion and those with atherosclerotic occlusion or severe stenosis: 28% of the former and 29% of the latter died during the first 24 hours after admission. The incidence of intraluminal thrombotic occlusion of surgically excised, failed aortocoronary vein grafts was 42 (66%) in 64 patients with nonfibrotic, patent grafts. Most of these vessels were severely atherosclerotic. The presence of intraluminal thrombi in about half of patients who died of acute myocardial infarction and in two thirds of excised, nonfibrotic, previously patent vein grafts indicates how many patients may benefit from thrombolytic therapy.

(Kern WH: Intraluminal thrombosis of coronary arteries in fatal myocardial infarctions and in failed aortocoronary saphenous vein grafts. West J Med 1988 Oct; 149:426-428)

Since the initial clinical-pathologic correlation of coronary artery thrombosis and acute myocardial infarction in 1912 by Herrick,[1] the significance of coronary artery thrombosis has been well recognized and has been the subject of numerous studies. Reports in the 1960s and early 1970s[2-4] that coronary artery thrombosis may be the result rather than the cause of myocardial infarction may have delayed the use of thrombolytic agents in the treatment of early acute myocardial infarction.[5] The current concept is again that thrombotic coronary artery occlusion, usually complicating atheromatous plaques, is frequently the cause of transmural and, less often, subendocardial infarction.[6] It is generally held that significant narrowing of a coronary artery by an atheromatous plaque causes angina and that acute ischemic syndromes are initiated by plaque injury. With intraluminal thrombosis, acute myocardial infarction may develop.[7] It has been reported that the vast majority of patients with acute myocardial infarction during the first hours have a coronary artery that is totally occluded, usually by a thrombus,[8] and that most patients who die in less than six hours have an intraluminal thrombus.[9] If intraluminal thrombosis is indeed a common or perhaps the most common cause of acute infarction, thrombolytic therapy should be beneficial although it may not be effective in patients with the also common intraintimal hemorrhages into a damaged atheromatous plaque[9] and in those with atheromatous stenosis or occlusion without thrombosis.

At the same time, the examination of surgically excised, failed, aortocoronary saphenous vein bypass grafts in this laboratory[10] and elsewhere[11,12] has revealed a high incidence of thrombotic occlusion. Patients who underwent a coronary artery bypass operation in the past and again become symptomatic may therefore also benefit from thrombolytic therapy.

To determine the incidence of intraluminal thrombosis in the coronary arteries of patients who died after hospital admission of acute myocardial infarction and in the surgically excised, failed aortocoronary bypass grafts of patients who underwent a repeat coronary artery bypass graft procedure, the records and slides from these cases were reviewed.

Patients and Methods

The autopsy protocols of all patients who died of acute myocardial infarction at the Hospital of the Good Samaritan (Los Angeles) from January 1, 1953, to November 30, 1987, were reviewed. Patients who had had previous vein grafts or other cardiac surgical procedures were excluded. The site and degree of stenosis were recorded for the principal coronary arteries. Whether the occlusion was caused by thrombosis or by atherosclerotic changes was noted. All sections of the coronary arteries were examined. The number of available sections varied, but the gross descriptions and microscopic findings allowed a classification in each case. Narrowing of 75% or more was considered severe stenosis. The presence of intraluminal or intraintimal and plaque hemorrhage was noted, and the duration of a patient's survival after admission to hospital was recorded and tabulated.

The sections of all aortocoronary saphenous vein bypass grafts that had been surgically excised between July 1, 1971, and August 30, 1987, were also examined. Not all failed grafts were excised during repeat coronary artery bypass graft procedures, but cross sections from all excised vessels

From the Department of Pathology, Hospital of the Good Samaritan, Los Angeles. Ms Andrea Smith Sprole and John Viggiano, MD, assisted in the review and tabulation of the case material.

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were available, and most have been sectioned in toto. The pathologic findings were categorized and the incidence of intraluminal thrombosis was noted in relation to the underlying pathologic changes in the vessel wall.

Results

A total of 648 autopsies of fatal cases of acute myocardial infarction were reviewed. The gross and microscopic findings were of intraluminal coronary artery thrombosis in 314, or 48% of the cases. Cases of sudden death that occurred before the patient could be admitted are not included, but the review shows that 28% of the deaths occurred during the first 24 hours after admission, 39% during the second to seventh day, and about a third after seven days or longer (Table 1). There was no appreciable difference in the length of survival between patients with coronary artery thrombosis and those with atherosclerotic occlusion or severe stenosis, and, conversely, there was no difference in the incidence of thrombosis between patients who died soon after admission and those who survived for a week or longer.

Only cases in which thrombotic material was present within the remaining generally stenosed lumina were classified as showing thrombosis. Many other cases showed the presence of old or recent hematomas within plaques but no associated intraluminal thrombosis. These were categorized as atherosclerotic lesions.

As Table 2 shows, the left anterior descending coronary artery was involved by intraluminal thrombosis in 172 cases, or 55%. This percentage was even higher (73%) in the category of atherosclerotic stenosis or occlusion. In 193 (79%) of these cases, one or more additional major vessels were significantly diseased. The decision as to which vessel was principally involved was based on the degree of vascular occlusion and at times the location of the infarction. The left main coronary artery was involved in some cases but never in a case of single-vessel disease.

In all, 119 surgically excised aortocoronary saphenous vein bypass grafts from 83 patients were examined. The most significant and advanced lesions, including those specifically of intraluminal thrombosis, were recorded. In 19 of the 83 patients, the vein grafts were occluded by fibrous tissue, either as a consequence of early thrombosis soon after the initial surgical procedure or possibly by progressive intimal fibrosis.[10] In ten cases, the vessels showed fibrointimal circumferential proliferation without atherosclerotic changes and were occluded by thrombi. In 32 of 54 cases, the grafts were involved by severe atherosclerosis and were completely occluded by intraluminal thrombi. Overall, 42 of 64 grafts (66%) that were not occluded by fibrosis did contain recently formed thrombi.

The two groups of cases are not clinically comparable. All autopsies were done in cases of acute myocardial infarction. Most patients with failed bypass grafts had angina as their principal symptom. Of 30 patients in whom the clinical findings were analyzed, 17 had stable angina, and 7 other patients had unstable angina. Only three had suffered a myocardial infarction during the three months preceding the operation. Despite this heterogeneity, thrombosis was a frequent and important finding in both groups.

TABLE 1.—*Coronary Artery Lesions in Fatal Acute Myocardial Infarctions*

Lesion	Total Number	Total (Percent)	Survival <24 h	Survival 24-72 h	Survival 3-7 d	Survival >7 d
Intraluminal thrombotic occlusion	314	(48%)	87	62	61	104
Atherosclerotic occlusion or severe stenosis	334	(52%)	98	66	63	107
All cases	648		185	128	124	211

Comment

The presence of intraluminal thrombi in 48% of our 648 autopsy cases of fatal acute myocardial infarction is similar to that reported in the literature, with a range of 38% to 54% in various series.[13] This is considerably less than the incidence of thrombosis assumed to be present in early stages of acute myocardial infarction based on angiographic studies.[8,13] Our cases do not include patients who died before they could be admitted to hospital but neither do reported cases that were examined by angiography. The fact that in our series the incidence of thrombosis was the same in patients who died within 24 hours and those who survived for several days raises questions about the reported high rate of thrombosis during the first hours of infarction. Earlier reports actually indicated a lower rate of thrombosis in early stages of myocardial infarction,[2] an observation that has not been substantiated by subsequent studies.[6]

The incidence of intraluminal thrombosis in surgically excised aortocoronary saphenous vein bypass grafts in our series is higher than that generally reported in the literature.[11,12,14]

It is important to keep in mind that thrombosis in coronary arteries and in most vein grafts is intimately associated with and generally is a complication of advanced atherosclerosis.[6,7] It has been proposed that coronary artery thrombosis may be due to spasms.[8,13] This may be the case, but there is unequivocal morphologic evidence that most intraluminal thrombi are associated with plaque injury such as intraplaque or intraintimal hemorrhage, fissuring, or rupture.[6,7,9,15] Sections frequently show an admixture of atheromatous material with an intraluminal thrombus. This may make it difficult to distinguish morphologically an actual intraluminal thrombus from hemorrhage into an atheromatous plaque. Such a distinction is, however, important to determine or at least estimate how many patients might benefit from thrombolytic therapy. Prompt treatment with tissue plasminogen activator is now widely advocated and is given

TABLE 2.—*Principal Involvement of Major Coronary Arteries*

Coronary Artery	Thrombosis, Number	Multivessel Disease, Number	Multivessel Disease, (Percent)	Atherosclerosis, Number	Multivessel Disease, Number	Multivessel Disease, (Percent)
Left anterior descending	172	91	(53)	245	193	(79)
Left circumflex	30	20	(67)	24	15	(62)
Right coronary	112	69	(62)	65	41	(63)

without a preceding arteriography.[16] It is doubtful that such therapy is effective in cases of "intraintimal" hemorrhage or thrombus.[9] Based on the review of the large number of cases in our series, it appears that thrombolytic therapy might have been effective in approximately half of our patients with acute myocardial infarction.

Studies of surgically excised aortocoronary saphenous vein bypass grafts show the development of atherosclerosis at a much more rapid rate than is seen in coronary arteries where significant atherosclerotic changes generally do not appear before the fourth decade. Smooth muscle cells, some including lipid vacuoles that correspond to early atherosclerotic changes in fatty streaks, were found in the thickened intima of grafted veins by electron microscope after 21 months,[17] and advanced atherosclerotic lesions were reported in grafted veins after 16 and 29 months.[17,18] Significant atherosclerosis usually develops five years after the placement of veins in the arterial circulation,[10,11] and failure of the grafts and recurrent angina or myocardial infarction are frequently associated with this process. The thrombosis in vein grafts that had undergone atherosclerotic changes was demonstrably associated with fissured or ruptured plaques and often with intraintimal hemorrhage into atheromas.[10] Thrombolytic therapy may therefore be indicated in these patients as well as in those with acute myocardial infarction.

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Medical Progress

Obesity
Part I—Pathogenesis

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Obesity—defined by a body mass index above 30 kg per m²—is a major problem for affluent nations. Its prevalence is higher in North America than in Europe—between 9% and 12% of the population. Reduced energy expenditure from exercise or metabolism or both may be an important contributory factor in the development of obesity because of a failure to reduce food intake sufficiently to maintain energy balance. A high ratio of abdominal circumference relative to gluteal circumference carries a twofold or greater risk of heart attack, stroke, hypertension, diabetes mellitus, gallbladder disease, and death. The effect of increased quantities of abdominal fat is greater than that of a similar increase in total body fat on the risks of ill health associated with obesity. Genetic factors appear to contribute about 25% to its etiology.

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The importance of obesity as a health problem can be highlighted by four statistics. Based on the changes in levels of cholesterol, glucose, blood pressure, and uric acid associated with spontaneous changes in body weight, Kannel and Gordon have estimated that "if everyone were at optimal weight there would be 25% less coronary heart disease and 35% less congestive failure and brain infarction."[1] If persons with diabetes mellitus who are obese were to attain normal weight and ameliorate their diabetes, the annual reduction in cost from hemodialysis for renal failure might be $200 million per year. Waaler has indicated that if body mass of the population became normal, this would produce a "total reduction [in mortality] of 15% corresponding to 3 years of added life expectancy."[2] Finally, Hannon and Lohman[3] have calculated the total amount of fossil fuel that would be equivalent to the food calories saved by overweight persons reducing to an optimal weight. Their calculations went as follows: adult Americans carry an excess of 2.3 billion pounds of fat. If these calories were used for daily metabolic needs, the reduced intake of food would be the equivalent of 1 to 3 billion gallons of gasoline. Such a saving in energy would supply more than the electrical demands for residences in Boston, Chicago, San Francisco, and Washington, DC.

Definition and Measurement of Body Fat and Its Distribution

If obesity can be this important, then we need to have a clear definition of the factors that produce this problem and its attendant risks. "Overweight" is an increase of body weight above some arbitrary standard defined in relation to height. To be obese, on the other hand, means to have an abnormally high proportion of body fat. To determine whether a person is obese or simply overweight because of increased muscle mass—as found in athletes—one needs techniques and standards for quantitating body fat. Several approaches to this problem are listed in Table 1, which also includes an estimate of the cost, ease of use, and accuracy of these methods.

Direct Analysis of Body Composition

Analyzing cadavers has provided basic information about body composition.[4] Water is the main component, accounting for about 60% to 65% of body weight.[5] Adipose tissue accounts for about 28% of body weight in men and 40% in women. When the mass of fat tissue is subtracted from total weight, the percentage of other components is similar in men and women.[4] Because direct carcass analysis cannot be done under normal circumstances, investigators have used indirect methods for measuring body composition and estimating the percentage of fat.

Indirect Analysis of Body Composition

Visual. A superficial analysis of fatness may be done by self-examination or through a visual inspection by another person. Increased bulging of skin folds or excessive roundness suggests in most instances increased fatness. Although such observations provide a good individual guide, they are not quantitative. One solution to this problem is the assignment of body types using photographs of persons without clothes.[6] With this technique, called somatotyping, the degree of endomorphy (roundness), mesomorphy (muscularity), and ectomorphy (leanness) can be given numeric values.

Anthropometric. Anthropometric measurements include height and weight; circumference of the chest, waist, hips, or extremities; diameter of the iliac crest, greater trochanters, or acromioclavicular joints; and skin-fold thickness (Table 1). Of these, the most widely used are height and weight, from which relative weight can be calculated. Relative weight is the actual body weight divided by a standard or "desirable" weight based on height. Thus, a man who is 178

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TABLE 1.—*Methods of Estimating Body Fat and Its Distribution*

Method	*Cost*	*Ease of Use*	*Accuracy*	*Measures Regional Fat*
Height and weight	$	Easy	High	No
Skin folds	$	Easy	Low	Yes
Circumferences	$	Easy	Moderate	Yes
Density				
Immersion	$$	Moderate	High	No
Plethysmograph	$$$	Difficult	High	No
Heavy water				
Tritiated	$$	Moderate	High	No
Deuterium oxide, or heavy oxygen	$$	Moderate	High	No
Potassium isotope (^{40}K)	$$$	Difficult	High	No
Conductivity, total body electrical	$$$	Moderate	High	No
Bioelectric impedance	$$	Easy	High	No
Fat-soluble gas	$$	Difficult	High	No
Computed tomography	$$$$	Difficult	High	Yes
Ultrasonography	$$$	Moderate	Moderate	Yes
Neutron activation	$$$$	Difficult	High	No
Magnetic resonance	$$$$	Difficult	High	Yes

$=low cost, $$=moderate cost, $$$=high cost, $$$$=very high cost

TABLE 2.—*Body Weights in Kilograms According to Height and Body Mass Index**†

	Body Mass Index, kg/m²													
Height, cm	*19.0*	*20.0*	*21.0*	*22.0*	*23.0*	*24.0*	*25.0*	*26.0*	*27.0*	*28.0*	*29.0*	*30.0*	*35.0*	*40.0*
	Body Weight, kg													
140.0	37.2	39.2	41.2	43.1	45.1	47.0	49.0	51.0	52.9	54.9	56.8	58.8	68.6	78.4
142.0	38.3	40.3	42.3	44.4	46.4	48.4	50.4	52.4	54.4	56.5	58.5	60.5	70.6	80.7
144.0	39.4	41.5	43.5	45.6	47.7	49.8	51.8	53.9	56.0	58.1	60.1	62.2	72.6	82.9
146.0	40.5	42.6	44.8	46.9	49.0	51.2	53.3	55.4	57.6	59.7	61.8	63.9	74.6	85.3
148.0	41.6	43.8	46.0	48.2	50.4	52.6	54.8	57.0	59.1	61.3	63.5	65.7	76.7	87.6
150.0	42.8	45.0	47.3	49.5	51.8	54.0	56.3	58.5	60.8	63.0	65.3	67.5	78.8	90.0
152.0	43.9	46.2	48.5	50.8	53.1	55.4	57.8	60.1	62.4	64.7	67.0	69.3	80.9	92.4
154.0	45.1	47.4	49.8	52.2	54.5	56.9	59.3	61.7	64.0	66.4	68.8	71.1	83.0	94.9
156.0	46.2	48.7	51.1	53.5	56.0	58.4	60.8	63.3	65.7	68.1	70.6	73.0	85.2	97.3
158.0	47.4	49.9	52.4	54.9	57.4	59.9	62.4	64.9	67.4	69.9	72.4	74.9	87.4	99.9
160.0	48.6	51.2	53.8	56.3	58.9	61.4	64.0	66.6	69.1	71.7	74.2	76.8	89.6	102.4
162.0	49.9	52.5	55.1	57.7	60.4	63.0	65.6	68.2	70.9	73.5	76.1	78.7	91.9	105.0
164.0	51.1	53.8	56.5	59.2	61.9	64.6	67.2	69.9	72.6	75.3	78.0	80.7	94.1	107.6
166.0	52.4	55.1	57.9	60.6	63.4	66.1	68.9	71.6	74.4	77.2	79.9	82.7	96.4	110.2
168.0	53.6	56.4	59.3	62.1	64.9	67.7	70.6	73.4	76.2	79.0	81.8	84.7	98.8	112.9
170.0	54.9	57.8	60.7	63.6	66.5	69.4	72.3	75.1	78.0	80.9	83.8	86.7	101.2	115.6
172.0	56.2	59.2	62.1	65.1	68.0	71.0	74.0	76.9	79.9	82.8	85.8	88.8	103.5	118.3
174.0	57.5	60.6	63.6	66.6	69.6	72.7	75.7	78.7	81.7	84.8	87.8	90.8	106.0	121.1
176.0	58.9	62.0	65.0	68.1	71.2	74.3	77.4	80.5	83.6	86.7	89.8	92.9	108.4	123.9
178.0	60.2	63.4	66.5	69.7	72.9	76.0	79.2	82.4	85.5	88.7	91.9	95.1	110.9	126.7
180.0	61.6	64.8	68.0	71.3	74.5	77.8	81.0	84.2	87.5	90.7	94.0	97.2	113.4	129.6
182.0	62.9	66.2	69.6	72.9	76.2	79.5	82.8	86.1	89.4	92.7	96.1	99.4	115.9	132.5
184.0	64.3	67.7	71.1	74.5	77.9	81.3	84.6	88.0	91.4	94.8	98.2	101.6	118.5	135.4
186.0	65.7	69.2	72.7	76.1	79.6	83.0	86.5	89.9	93.4	96.9	100.3	103.8	121.1	138.4
188.0	67.2	70.7	74.2	77.8	81.3	84.8	88.4	91.9	95.4	99.0	102.5	106.0	123.7	141.4
190.0	68.6	72.2	75.8	79.4	83.0	86.6	90.3	93.9	97.5	101.1	104.7	108.3	126.4	144.4
192.0	70.0	73.7	77.4	81.1	84.8	88.5	92.2	95.8	99.5	103.2	106.9	110.6	129.0	147.5
194.0	71.5	75.3	79.0	82.8	86.6	90.3	94.1	97.9	101.6	105.4	109.1	112.9	131.7	150.5
196.0	73.0	76.8	80.7	84.5	88.4	92.2	96.0	99.9	103.7	107.6	111.4	115.2	134.5	153.7
198.0	74.5	78.4	82.3	86.2	90.2	94.1	98.0	101.9	105.9	109.8	113.7	117.6	137.2	156.8
200.0	76.0	80.0	84.0	88.0	92.0	96.0	100.0	104.0	108.0	112.0	116.0	120.0	140.0	160.0

*Each entry gives the body weight in kilograms (kg) for a person of a given height and body mass index.
†Desirable body mass index range in relation to age (from Bray[7]).

Age Group, yr	*Body Mass Index, kg/m²*	*Age Group, yr*	*Body Mass Index, kg/m²*
19-24	19-24	45-54	22-27
25-34	20-25	55-64	23-28
35-44	21-26	65+	24-29

cm tall (5′8″) and weighs 82 kg (180 lb) would have a desirable weight of 69.4 kg (153 lb) and a relative weight of 1.18 (82/69.4=1.18) or 118% of desirable weight.

The tables of desirable weight provided by the Metropolitan Life Insurance Company have received the widest use. They are divided into three subgroups based on frame size. No direct measures of frame size were made, however, when these data were collected. The upper and lower frame sizes appear to be the upper and lower quarters (quartiles) of the population, with the medium frame representing the middle two quarters. The newest tables, published in 1983, provide a higher weight range than the older tables, and there has been a reluctance on the part of many to use the newer life insurance tables.

Weight and height can also be related by various ratios. These include wt/ht, $ht/(wt)^{1/3}$ (Ponderal index), or $wt/(ht)^P$. When P=2 in this latter expression, $wt/(ht)^2$ is called the body mass or Quetelet index (kg per m^2). The correlation of these indices with body fat measured from body density ranges between 0.7 and 0.8.[6] Because the body mass or Quetelet index has the best correlation with body fat, it is preferred. Tables 2 and 3 show the body mass indices for various height and weight categories.

The desirable range of body weights for each height appears to increase slightly with age.[7] These ranges are listed in Tables 2 and 3. The body mass or Quetelet index can also be used to assess the magnitude of potential health risks associated with being overweight, and it may be used as a guide to therapy.

The degree of body fat or obesity measured with the use of specially designed calipers can be assessed from the thickness of skin folds. Regression equations are available that calculate the amount of body fat from skin-fold thicknesses measured at several sites.[8] One difficulty with skin-fold measurements is that the equations used to estimate body fat are related to age, sex, and ethnic background. Body fat increases with age even though the sum of the skin folds remains constant.[9] This implies that the accumulation of fat with age occurs in large part at sites other than subcutaneous ones. There are also sex and ethnic differences in the distribution of body fat.

The ratio of waist or abdominal circumference to the hip or gluteal circumference provides an index of the regional distribution of body fat and has proved valuable as a guide to health risks. A nomogram for obtaining the abdominal-gluteal ratio (android-gynoid ratio) or waist-hips ratio is shown in Figure 1. The circumference of the waist is measured at the narrowest area above the umbilicus; the hip circumference is at the maximal gluteal protrusion. Abdominal fat (high android-gynoid ratio) is characteristic of men and is referred to as android or upper body obesity. Fat on the hips is typical for women and is referred to as gynoid or lower body fat distribution. The percentile values for these for men and women in relation to age are shown in Figure 2. Persons with values above the 10th percentile are at high risk for adverse health consequences, as we will discuss in more detail later.

Isotopic or chemical measurement of body compartments. A more quantitative approach to measuring body composition is to use one of several dilutional techniques. The most direct method is with fat-soluble agents, such as cyclopropane or krypton, whose distribution can be related to total fat (Table 1). The equilibration time is long, however, and special equipment is needed, thus making this method expensive. The second approach is to calculate body fat from measuring body water using tritiated water (^3H_2O), deuterated water (D_2O), or water with heavy oxygen ($H_2{}^{18}O$),[5,10] all of which equilibrate with body water. Lean body mass is

TABLE 3.—*Body Weights in Pounds According to Height and Body Mass Index**†

Height, in	Body Mass Index, kg/m²													
	19.0	20.0	21.0	22.0	23.0	24.0	25.0	26.0	27.0	28.0	29.0	30.0	35.0	40.0
	Body Weight, lb													
58.0	90.7	95.5	100.3	105.0	109.8	114.6	119.4	124.1	128.9	133.7	138.5	143.2	167.1	191.0
59.0	93.9	98.8	103.8	108.7	113.6	118.6	123.5	128.5	133.4	138.3	143.3	148.2	172.9	197.6
60.0	97.1	102.2	107.3	112.4	117.5	122.6	127.7	132.9	138.0	143.1	148.2	153.3	178.8	204.4
61.0	100.3	105.6	110.9	116.2	121.5	126.8	132.0	137.3	142.6	147.9	153.2	158.4	184.8	211.3
62.0	103.7	109.1	114.6	120.0	125.5	130.9	136.4	141.9	147.3	152.8	158.2	163.7	191.0	218.2
63.0	107.0	112.7	118.3	123.9	129.6	135.2	140.8	146.5	152.1	157.7	163.4	169.0	197.2	225.3
64.0	110.5	116.3	122.1	127.9	133.7	139.5	145.3	151.2	157.0	162.8	168.6	174.4	203.5	232.5
65.0	113.9	119.9	125.9	131.9	137.9	143.9	149.9	155.9	161.9	167.9	173.9	179.9	209.9	239.9
66.0	117.5	123.7	129.8	136.0	142.2	148.4	154.6	160.8	166.9	173.1	179.3	185.5	216.4	247.3
67.0	121.1	127.4	133.8	140.2	146.5	152.9	159.3	165.7	172.0	178.4	184.8	191.1	223.0	254.9
68.0	124.7	131.3	137.8	144.4	151.0	157.5	164.1	170.6	177.2	183.8	190.3	196.9	229.7	262.5
69.0	128.4	135.2	141.9	148.7	155.4	162.2	168.9	175.7	182.5	189.2	196.0	202.7	236.5	270.3
70.0	132.1	139.1	146.1	153.0	160.0	166.9	173.9	180.8	187.8	194.7	201.7	208.6	243.4	278.2
71.0	135.9	143.1	150.3	157.4	164.6	171.7	178.9	186.0	193.2	200.3	207.5	214.6	250.4	286.2
72.0	139.8	147.2	154.5	161.9	169.2	176.6	183.9	191.3	198.7	206.0	213.4	220.7	257.5	294.3
73.0	143.7	151.3	158.8	166.4	174.0	181.5	189.1	196.7	204.2	211.8	219.3	226.9	264.7	302.5
74.0	147.7	155.4	163.2	171.0	178.8	186.5	194.3	202.1	209.9	217.6	225.4	233.2	272.0	310.9
75.0	151.7	159.7	167.7	175.6	183.6	191.6	199.6	207.6	215.6	223.5	231.5	239.5	279.4	319.4
76.0	155.8	164.0	172.2	180.4	188.6	196.8	205.0	213.2	221.4	229.5	237.7	245.9	286.9	327.9

*Each entry gives the body weight in pounds (lb) for a person of a given height and body mass index.
†Desirable body mass index range in relation to age (from Bray[7]).

Age Group, yr	Body Mass Index, kg/m²	Age Group, yr	Body Mass Index, kg/m²
19-24	19-24	45-54	22-27
25-34	20-25	55-64	23-28
35-44	21-26	65+	24-29

usually assumed to be 72% water, although this assumption may be in error in children and in very obese persons, since the water content of the non-fat part of adipose tissue is 85%. Body "cell mass" can also be quantitated by measuring the amount of the naturally occurring isotope of potassium (^{40}K) in the body (Table 1). For this measurement, the lean body mass is usually assumed to contain 63 mEq of K^+ per kg.[10] Once lean body mass has been determined, body fat can be calculated as follows:

$$\text{body fat} = (\text{body weight}) - (\text{lean body mass})$$

Body density and body volume. Measuring the body density provides a quantitative technique for measuring body fat and fat-free mass. Density is determined from the weight of the body in and out of water using Archimedes' principle.[5,8] In this procedure, a person is weighed both underwater and out of water, and the residual volume of the lungs is determined. With this information, it is possible to fractionate the body into its fat and nonfat components, assuming a density for fat of 0.9 grams per cm^3. This technique is relatively easy if appropriate facilities are available, but it remains primarily a research method.

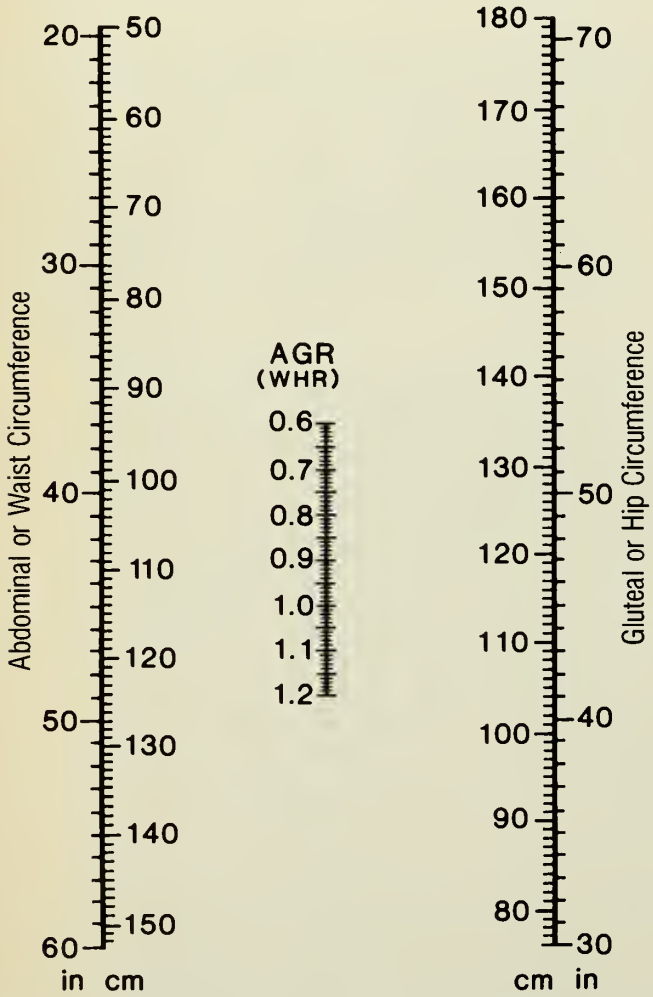

Figure 1.—The abdominal (waist) to gluteal (hips) ratio (AGR) can be determined by placing a straight edge between the column for waist circumference and the column for hip circumference and reading the ratio from the point where this straight edge crosses the AGR or waist-hips ratio (WHR) line. The waist or abdominal circumference is the smallest circumference below the rib cage and above the umbilicus, and the hips or gluteal circumference is taken as the largest circumference at the posterior extension of the buttocks.

Other. Ultrasound waves applied to the skin will be reflected by the fat, muscle, and other tissues and can provide a measure of fat thickness.[11] Electromagnetic conductivity or total body electrical conductivity can also be used to quantitate lean and fat tissue because of differences in their ability to conduct electromagnetic waves.[12] A relatively inexpensive instrument for measuring body fat uses bioelectric impedance analysis. Electrodes are applied to an arm and leg and the impedance (reciprocal of conductance) is measured. Because impedance is related to the aqueous portion of the body, formulas can be developed to estimate the percentage of fat in the body. These formulas provide good estimates of the percentage of body fat in normal weight persons,[13] but the validation in obese subjects is less adequate. Computed tomographic scans and magnetic resonance imaging provide pictures from which the thickness of fat can be determined. The advantage of the computed tomographic scan is that it provides quantitative estimates of regional fat and can give a

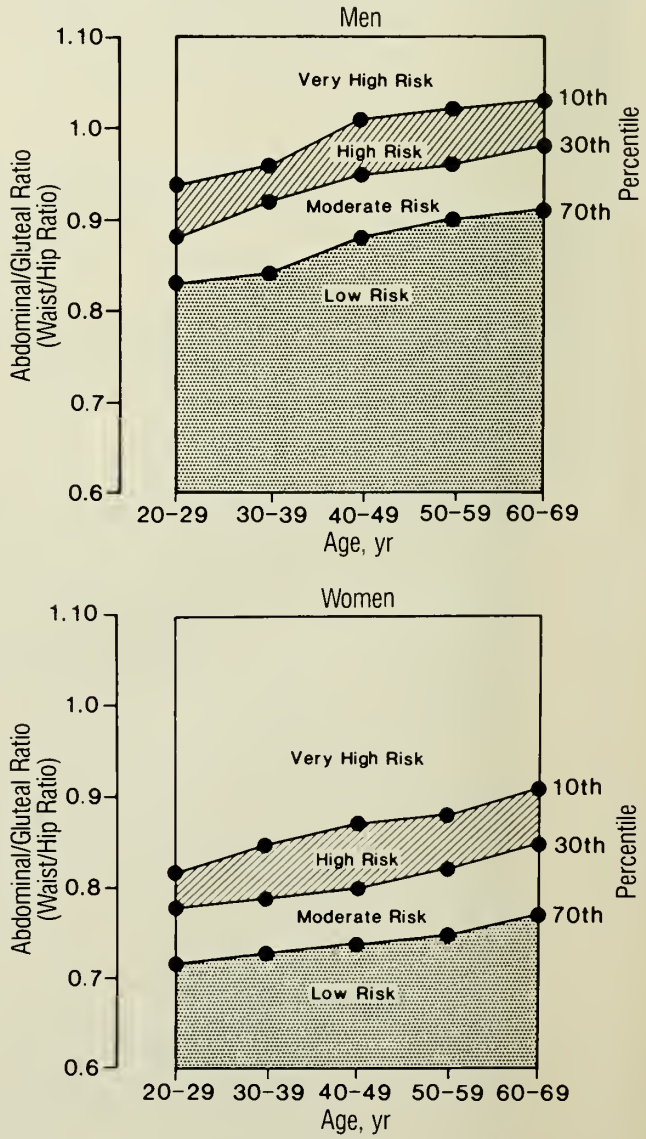

Figure 2.—The percentiles for the ratio of abdominal circumference to gluteal circumference (ratio of waist to hips) are shown for men **(top panel)** and women **(bottom panel)** by age groups. The relative risk for these percentiles is indicated based on the available information. (Plotted from tabular data in the Canadian Standardized Test of Fitness, Third Edition 1986 [available from Fitness and Amateur Sport Canada, 365 Laurier Ave W, Ottawa, Ontario K1A OX6].)

ratio of intra-abdominal to extra-abdominal fat.[14] Because fat distribution and possibly the relative amount of intra-abdominal to subcutaneous fat relate to the health risks of obesity, this technique may become more widely used. Its disadvantages, however, are that there is radiation exposure during the measurement and the equipment is expensive (Table 1). Finally, neutron activation of the whole body can be used to identify chemical components by their emission spectra.[15]

Using one or more of these techniques, the major components of the body can be determined. The proportions of fat and nonfat components for a normal (70 kg) and obese (100 kg) man and a corresponding woman are shown in Figure 3. The extra 30 kg of weight is assumed to be two-thirds fat, which adds a little more than half to body weight but increases energy stored as fat by 200%.

In summary, body fat can be estimated in many ways, but the most accurate methods are not widely available or are expensive. From a practical point of view, three methods are most useful. Measurements of height and weight, preferably expressed as the body mass index, provide an estimate of degree of overweight. Measuring impedance may also prove useful in estimating total fat. For regional fat distribution, the use of the circumference at the abdomen or waist and the gluteus or hips has been useful, but measuring skin folds on the trunk and extremities—particularly the subscapular skin fold—would also appear to be useful.

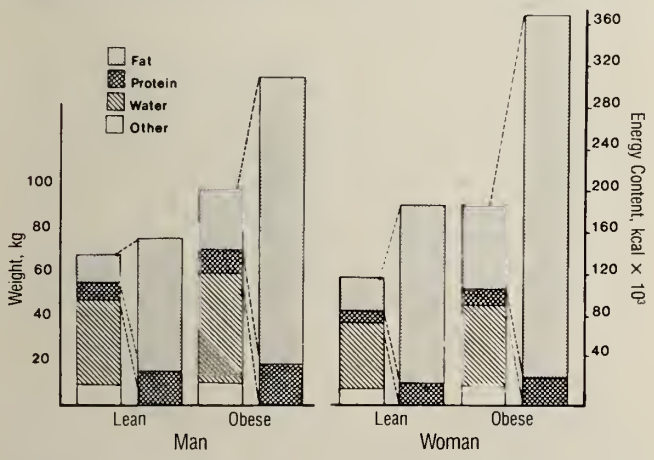

Figure 3.—The percentage of fat, protein, water, and other components for a normal 70-kg man and a 55-kg woman is shown at the left of each group, along with the data for an obese person who is 30 kg heavier in the middle. The contribution of fat and protein to body energy stores is indicated in the bars to the right.

Prevalence of Obesity

A number of factors influence body fat, including age, sex, race, and physical activity. At birth the human body contains about 12% fat, a content that is higher than in any other mammal except the whale. During the newborn period, the body fat content rises rapidly to reach a peak of about 25% at 6 months of age and then declines to 15% to 18% in the prepubertal years. At puberty there is a notable increase in the percentage of fat in girls and a notable decrease in boys. By age 18 boys have about 15% to 18% body fat and girls, 20% to 25%. The amount of body fat increases in both sexes after puberty and during adult life rises to between 30% and 40% of body weight. Between ages 20 and 50, the fat content in men approximately doubles and that in women increases by about 50%. Total body weight, however, rises by only 10% to 15%. The increased fat is accounted for in part by an increase in body weight and in part by a reduction in lean body mass.[5]

The composition of the body is also influenced by the level of physical activity.[16] During physical training, body fat usually decreases and lean tissue increases. After training ends, however, this process is reversed. These shifts between body fat and lean tissue can occur without any changes in body weight, but if regular activity is maintained throughout adult life, the increase in body fat that usually occurs even when body weight is stable may be prevented.

Racial differences in body weight (Figure 4) may exist, but it is often difficult to separate racial from environmental factors. Socioeconomic conditions, however, clearly play an important role in the development of obesity. Excess body weight is 7 to 12 times more frequent in women from lower social classes than in women from the upper social classes.[17] Among men, social class has a much smaller relationship to being overweight.

The patterns of body weight in men and women are changing. Data obtained at the time of evaluation for military service show that men inducted into the army in the 1950s were heavier than men of the same height drafted in 1943. The 1943 inductees were in turn heavier than those inducted in 1918.[5] The Framingham study shows similar changes for men but suggests that women may not be getting fatter.[1]

Using the body mass index, it is possible to compare the

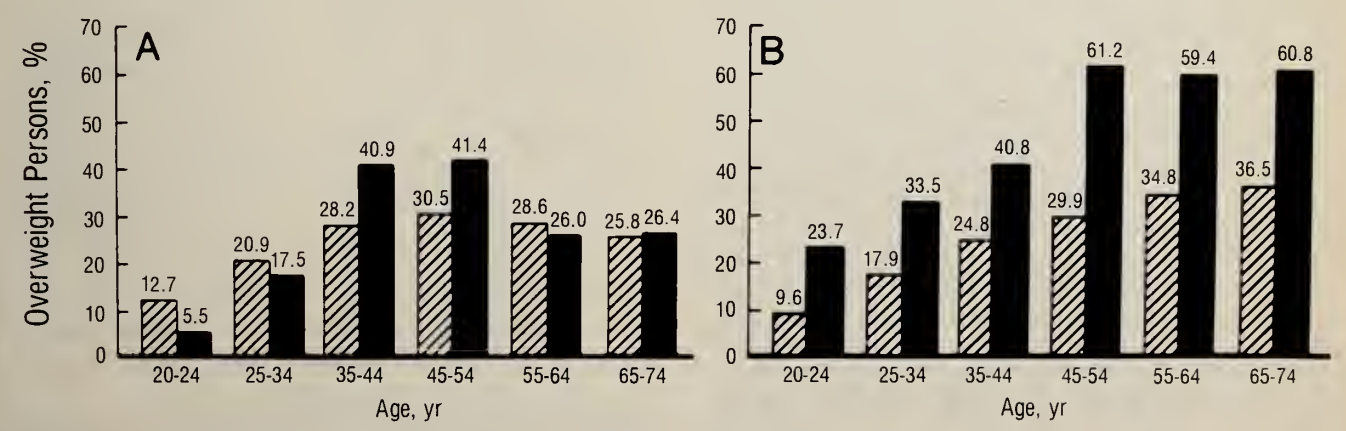

Figure 4.—Data from the National Center for Health Statistics show the percentage of overweight men **(A)** and women **(B)** by age and race using the 85th percentile of weights for height of 20- to 24-year-olds as the upper limits for weight (from Van Itallie[18]). The crosshatched bars show percentages for whites, the solid bars those for blacks.

TABLE 4.—*Percentage of Overweight and Obese Persons in Several Affluent Countries**

	Age, yr	Overweight, % Men	Overweight, % Women	Obese, % Men	Obese, % Women
United States	20-74	31	24	12	12
Canada	20-69	40	28	9	12
Great Britain	16-65	34	24	6	8
The Netherlands	20+	34	24	4	6
Australia	25-64	34	24	7	7

*Adapted from Bray.[19]

prevalence of obesity in several countries (Table 4).[18,19] The prevalence of persons with a body mass index of 25 to 30 kg per m^2 is almost identical in all populations. The higher percentage of men in the range of 25 to 30 kg per m^2 results from the fact that the median body mass index for women is 22 kg per m^2, whereas for men it is 25 kg per m^2. The prevalence of those with a body mass index above 30 kg per m^2 is, however, higher in both the United States and Canada than in Great Britain, the Netherlands, or Australia. There are at least three possible explanations for this. First, the higher proportion of automobiles in North America might substantially reduce energy expenditure. Second, there might be differences in quantity or quality of dietary intake. Third, higher rates of smoking might explain the lower rates of obesity outside North America. Obesity is also prevalent in many other populations, suggesting its worldwide importance.[20]

Pathogenesis of Obesity

Nutrient Imbalance

Food intake. Obesity is a problem of nutrient imbalance—more foodstuffs are stored as fat than are used for energy and metabolism. Do the obese eat more than lean subjects? Three general techniques have been used to obtain information about the energy intake of humans. These include the use of nutritional histories and records of food eaten, observing and measuring food choices in natural settings, and measuring food intake in a laboratory setting, with experimental changes in the nature of the food or the eating situation. Most surveys suggest that energy intake is significantly lower in the overweight than in those of normal weight.[21] One concern with these observations is the reliability of the study when the data are based on self-reports. Repeat dietary histories on obese patients during a three-month period showed an apparent underreporting of intake in the initial interview.[22] It may be that the accuracy of reporting becomes less reliable as excess weight increases.

In direct observations of food intake, obese persons chose or ate larger meals than did lean persons. In a variety of studies on food choice, Stunkard and Kaplan found relative uniformity in the size of meals chosen in natural settings.[23] The caloric content of the meals was strongly affected by the eating site, and there was great variability in the amount of food chosen at each site. Thus, the major influence on how much people chose to eat was where they ate. Eating in a cafeteria led to eating more food. A recent naturalistic study by Stunkard and Waxman indicated that obese adolescent boys ate more than did their lean siblings at school but not at home.[24]

Adjusting caloric intake to changes in the caloric concentration of the food eaten has produced a nearly uniform pattern in several laboratory studies. Obese persons failed to compensate for changes in caloric concentration as well as normal weight persons did.[25]

Energy requirements generally decline with age, and we would anticipate that food intake would show a corresponding decrease.[5] The values for caloric intake from three surveys are presented in Figure 5. The peak values occur in the second decade of life, followed by a gradual decline in successive decades for both sexes. Thus, the increase in body weight and body fat with age cannot be attributed to an increased nutrient intake but rather to a relatively greater reduction in energy expenditure.

In summary, objective measurements on obese subjects tend to support the conclusion that they choose and eat more food and often do so more rapidly than normal weight subjects. The data also suggest that retrospective observations of food intake may be biased on the low side, particularly in the obese. External environmental influences, such as lighting and noises, may modify the quantity and the quality of food eaten by obese persons more than it does in lean ones. Finally, increasing fatness with age appears to result from a greater reduction in energy expenditure because food intake also declines with age.

Energy expenditure. Total energy expenditure can be measured by a variety of methods.[5,26] Although some differences in terminology exist, the partition of energy expenditure can be shown as in Figure 6.

Resting metabolism is the total energy required by the body in a resting state and is influenced by age, sex, body weight, drugs, climate, and genetics. As shown in Figure 6, it represents about 70% of total energy expenditure. When corrected for body weight, the highest rate of energy expenditure occurs in infants. There is a gradual decline in childhood and a further slow decline in adult life. Metabolic rates for women are usually lower than those for men of comparable height and weight, primarily because of the higher

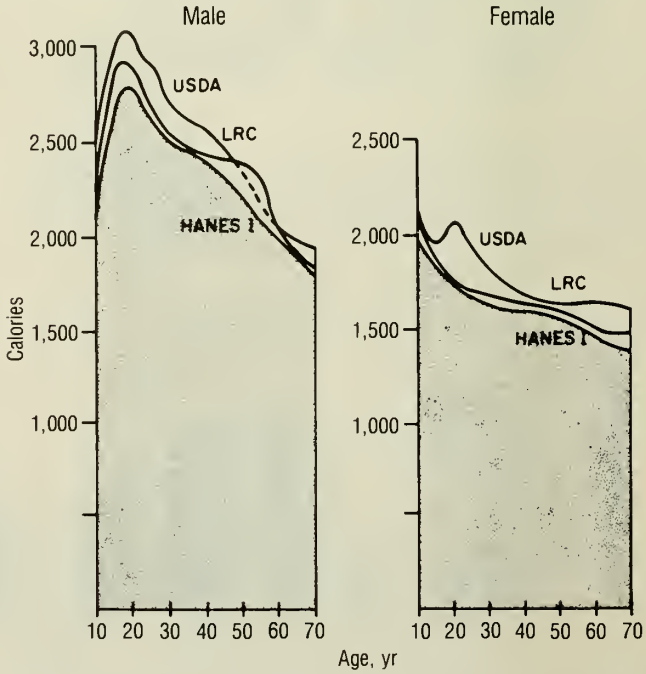

Figure 5.—Data from three studies of food intake in relation to age are plotted for men and women (from Bray[26]). HANES 1 = Health and Nutrition Examination Survey, LRC = Lipid Research Clinics, USDA = US Department of Agriculture

body fat content of women. The resting metabolic rate has the best relationship to fat-free body mass, but it is also closely related to surface area and total body weight because heat loss is related to the surface area of the skin. As body weight or lean body mass increases, there is a rise in the metabolic rate.[27-29] Figure 7 shows the 24-hour energy expenditure in relation to body weight. As weight rises, the energy expenditure also rises at a rate of about 22 kcal per kg of body weight.

Energy expenditure, even for persons with the same lean body mass or surface area, age, and sex, may vary as much as 20%. Thus, if the mean resting expenditure is 1,000 kcal per day^{-1}, then two persons of normal weight could differ by 400 kcal per day^{-1} (1,200 versus 800 kcal per day^{-1}).

In a careful study of the resting metabolic rate among family members, Bogardus and colleagues[29] showed that metabolic rate clustered in families. If one person was below the median for energy use, other members of the family also tended to be below the median. In longitudinal studies, these

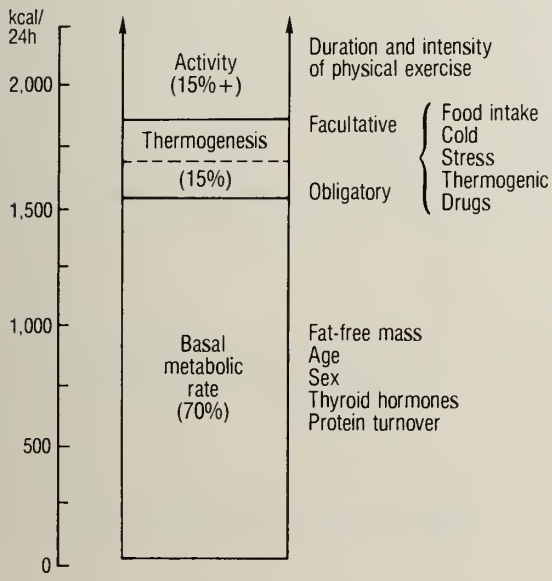

Figure 6.—The energy partition into basal energy needs, thermogenesis, and activity are estimated based on a 2,500-kcal-per-day requirement. The upper end is open, indicating that activity is variable and can be increased for a normal weight person. This usually involves about 30% of the total daily energy expenditure, however.

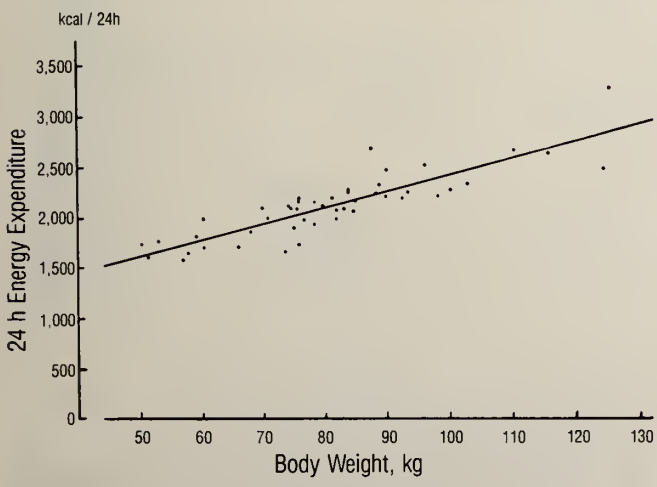

Figure 7.—As body weight rises, the metabolic rate increases. The slope of this relationship is approximately a 24-hour energy expenditure = (750 kcal) + (15 kcal per kg) (from Jequier and Schutz[27]).

same workers have found suggestive evidence that weight gain is more likely in those with lower metabolic rates in relation to lean body mass.[30]

The resting metabolic rate, then, is closely related to body weight, lean body mass, and body surface area. Obese persons tend to have an expanded lean body mass and thus greater resting metabolic rates than lean persons of similar heights. A low resting metabolic rate in relation to lean body mass may be a predictor for the onset of obesity.

Physical activity. There are two approaches to studying the relationship of physical activity to obesity. In the laboratory, the treadmill and the cycle ergometer have been the main tools used to examine the efficiency of exercising muscle in obese subjects. Lean persons before and after weight gain and notably obese persons have both been studied by bicycle ergometry.[26] The resting level of energy expenditure in massively obese subjects weighing in excess of 140 kg (285 lb) was twice that of lean subjects. In each group the efficiency for coupling energy production to muscular contraction was 30%. Moreover, the efficiency of coupling metabolism to muscular contraction remained the same following substantial weight gain in normal weight subjects.[26] We thus conclude that there is no evidence to indicate an abnormality in the metabolic coupling of substrate metabolism to the contraction of muscular tissue in moderately or massively obese persons.

The second approach to studying energy expenditures is that of naturalistic observation. Obese persons are often observed to be less active than those of normal weight, as documented by several techniques. When given a choice of an escalator or stairs, for example, the obese were more likely to take the escalator.[31]

A lower level of spontaneous movement does not necessarily imply reduced energy expenditure, however, since an overweight person uses more energy for any given movement.[26] In one approach to this problem, Waxman and Stunkard related movement to energy expenditure and found that obese boys expended more energy on the playground but similar amounts inside the home when compared with lean siblings.[32] It is thus not possible to conclude that spending less time in physical activity results in a reduction of energy expenditure. In normal weight persons, graded increases in physical activity have been reported to increase food intake. In the obese, however, changing the level of physical activity has much less effect on food intake.[33] There is, therefore, no evidence to implicate a decrease in energy expenditure because of physical inactivity in the pathogenesis of obesity.

Thermogenic effects of food. When food is eaten, the metabolic rate rises and then returns toward normal. This process requires several hours, and during this time the increase in energy expenditure can approximate 10% to 15% of the total caloric value of the food eaten. One explanation for this thermogenic response to a meal is that it results from enhanced activity of the sympathetic nervous system and its effect on brown adipose tissue.[34] If this is correct, then a reduction in sympathetic activity of obese subjects compared with lean ones may provide a mechanism for enhanced metabolic efficiency that might allow calories to be stored rather than burned. Although brown adipose tissue is important in rodents, its importance in adult humans has not yet been shown.[35]

The concept that an altered thermic response to food may serve as a mechanism for the storage of extra calories in

human obesity is intriguing and controversial.[36] Some investigators have found a difference between obese and lean persons in the energy produced following a meal; others, however, have found no such difference. The discrepancy may lie in the size of the meal eaten, in the techniques of recording, in the meal's palatability,[37] and in whether subjects had abnormal glucose tolerance. Golay and co-workers examined 55 subjects with varying degrees of obesity and impaired glucose tolerance, including those with diabetes mellitus.[38] The increment in energy expenditure was significantly lower in obese persons without diabetes and those with impaired glucose tolerance than in the normal volunteers.[38] In turn, the obese persons with diabetes had a smaller response than those of normal weight or obese persons without diabetes. There was a negative correlation between the degree of thermic response and circulating insulin.[38] These data suggest that there is an impairment in the thermic response to a meal in obese persons and that one mechanism associated with this change is the cephalic phase secretory response of the pancreatic system for releasing insulin.

Adipose Tissue

More than 90% of body energy is stored as triglyceride in adipose tissue. Protein and glycogen provide important but smaller quantities of energy. Adipose tissue has two principal functions: the synthesis and storage of fatty acids in triacylglycerols and the release of fatty acids as a source of metabolic fuel. Triglyceride is stored in fat cells that differ in size between one region of the body and another. There may be important regional differences in the total number of fat cells, and this number appears to vary in different types of obesity.[39]

The storage of fat in the first months of life occurs primarily by an increase in the size of already existing fat cells. By the end of the first year, fat cell size has nearly doubled, with little change in the total number,[40] both in children who become obese and in those who do not. In children who are lean, the size of the fat cells decreases after the first year of life. Obese children, on the other hand, retain throughout childhood the large fat cells that developed during the first year of life. Fat cells multiply in number throughout the growing years in a process that usually stops in adolescence. The number of fat cells in obese children increases more rapidly than that in lean children, reaching adult levels by 10 to 12 years of age.[40] Current evidence suggests that, after puberty, acute changes in body fat stores occur primarily by an increase in the size of adipocytes that already exist, with little or no change in the total number. Severe weight loss is likewise accomplished primarily by a reduction in the size of extant fat cells. Recent evidence suggests, however, that the number of fat cells may change in adult life.[41] A steady increase in body fat, on the one hand, may lead to an increase in the number of fat cells; conversely, a prolonged reduction in body fat may possibly lead to a decrease in the number of fat cells.[41]

Knowing the size, number, and distribution of fat cells may be useful in classifying obesity and in estimating the prognosis with different forms of therapy.[42] Substantially overweight persons almost always have hypercellular fat organs, whereas those with modest degrees of overweight may be hypercellular but are much more likely to have only an increase in fat cell size or hypertrophic obesity. The duration of weight loss that follows successful dietary treatment is shorter and the rate at which weight is regained is more rapid in persons with hypercellular obesity compared with those with hypertrophic obesity.[42]

Health Risks Associated With Obesity

Total Body Fat and Risk of Mortality

The risk of mortality from obesity can be evaluated only in prospective studies. Studies involving more than 750,000 subjects each, by the life insurance industry,[43,44] the American Cancer Society,[45] and one involving nearly the entire population of Norway[2] have yielded similar results that have been confirmed by numerous smaller, prospective evaluations of cardiac risk factors. This overall relationship is shown in Figure 8, which shows relative mortality rates for various deviations of body mass index.[45] The data show a J- or U-shaped curve, with the lowest mortality for both men and women occurring among persons somewhat below the average body mass index.[46] Deviations above and below this are associated with an increase in mortality risk. The effect on life expectancy of small deviations in weight, however, is small, and there is a wide range around the average body mass index in which it is impossible to discern any increase in mortality. At an index of 30 kg per m^2, the mortality has already increased, and above 40 kg per m^2 the curve becomes steep. It is also apparent that mortality increases when the body mass index falls to values below the minimum mortality level. A 1983 study examining mortality during 16 years of follow-up in 2,381 men and women in Scotland sheds further light on this point.[47] While mortality from lung cancer increased with decreasing fatness, mortality from cardiovascular disease increased with increasing fatness. Findings similar to these have led to the concept that the two limits of the U-shaped relationship between fatness or relative weight and mortality are due to different causes of death. Thus, some digestive and respiratory tract diseases compose the low-weight deaths, whereas cardiovascular diseases, diabetes, and gallbladder disease make up the high-weight causes of death.

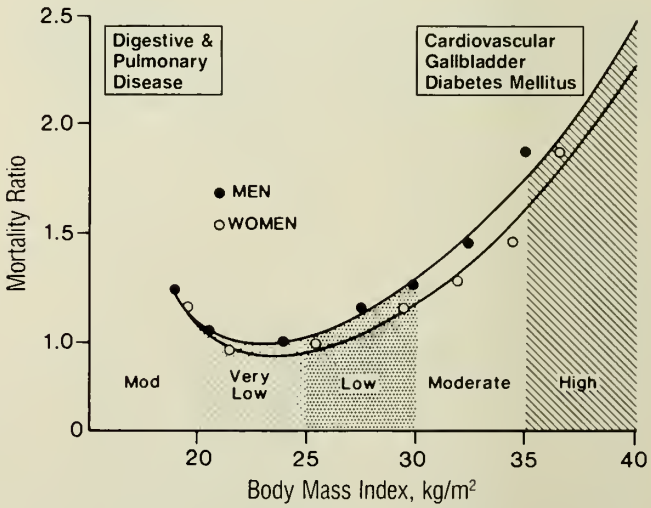

Figure 8.—Data from the American Cancer Society study have been plotted for men and women to show the relationship of body mass index to overall mortality risk. At a body mass index below 20 kg per m^2 and above 30 kg per m^2, there is an increase in relative mortality. The major causes for this increased mortality are listed, along with a division of body mass index groupings into various levels of risk (adapted from Lew and Garfinkel[45]).

Body Fat Distribution and Health Risks

One of the most important developments in understanding the health risks associated with obesity has been realizing the important role of body fat distribution. There are two types of fat distribution: the abdominal, android, upper body, or male type; and the gynoid, lower body, or female type. The former has a higher ratio of abdominal to gluteal circumference (android to gynoid ratio or waist-to-hip ratio). As early as the 1950s, Vague suggested that a preponderance of abdominal fat increases the risk for diabetes and cardiovascular disease.[48] Five prospective studies have examined the relation of fat distribution to morbidity and mortality.[49-53] Whether the ratio of abdominal to gluteal circumference, the subscapular skin fold, or a combination of skin folds was used as the indicator of abdominal fat, all five studies found a clear-cut and significant increase in the risk of death or an increased risk of diabetes mellitus, hypertension, or stroke. Fat distribution was a more important risk factor for morbidity and mortality than overweight or obesity per se and had a relative risk ratio of two or more. This is shown in data from a prospective study of residents of Gothenberg, Sweden (Figure 9). The data for waist-to-hips ratio divided into fifths of the population (quintiles) showed a much greater chance of remaining free of myocardial infarction and of long-term survival in the quintile with the lowest waist-to-hips ratio compared with the quintile with the highest waist-to-hips ratio.[49] This effect was independent of total fatness.

In addition to the prospective data described here, cross-sectional studies have also clearly shown an increased prevalence of glucose intolerance, insulin resistance, elevated blood pressure, and elevated blood lipid levels in both men and women with increased abdominal fat.[54,55] It has been suggested that the abdominal or android fat pattern may represent an increase in the size or number of more metabolically active intra-abdominal fat cells. These fat cells release free fatty acids directly into the portal circulation, which might interfere with insulin clearance in the liver and thus affect various metabolic processes. It is interesting to note in this context that a recent study from Japan used abdominal computed tomographic scanning of fat distribution to separate intra-abdominal or visceral fat from subcutaneous fat and thus defined a visceral-subcutaneous fat ratio. The visceral-subcutaneous ratio is correlated inversely with glucose tolerance.[56]

Obesity and Organ Function

Cardiovascular system. The relation of hypertension to obesity has been widely recognized. It is important to use a large enough cuff to measure the blood pressure in obese persons because a cuff that does not encircle 75% of the arm may artificially elevate the blood pressure.[57] Even with the limitations in the techniques of measuring blood pressure by indirect auscultation, however, the available data almost uniformly indicate the important relationship between body weight and blood pressure and between fat distribution and blood pressure (Figure 10).[58,59] The increased blood pres-

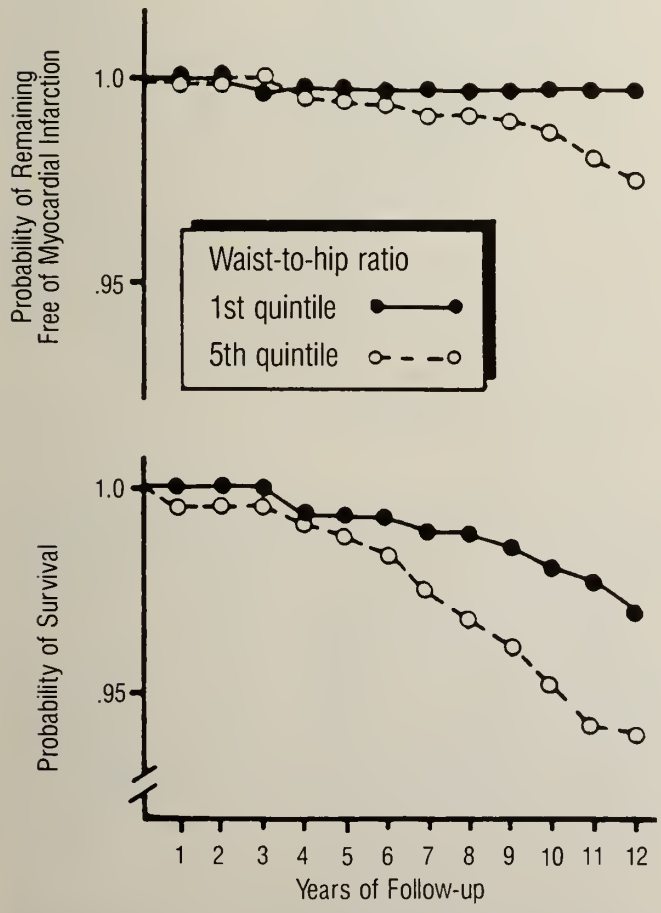

Figure 9.—These data show cumulative mortality in relation to abdominal (waist) to gluteal (hips) circumference ratio. They are from a prospective study of women in Gothenberg, Sweden, who were followed for 12 years (from Lapidus et al[49]).

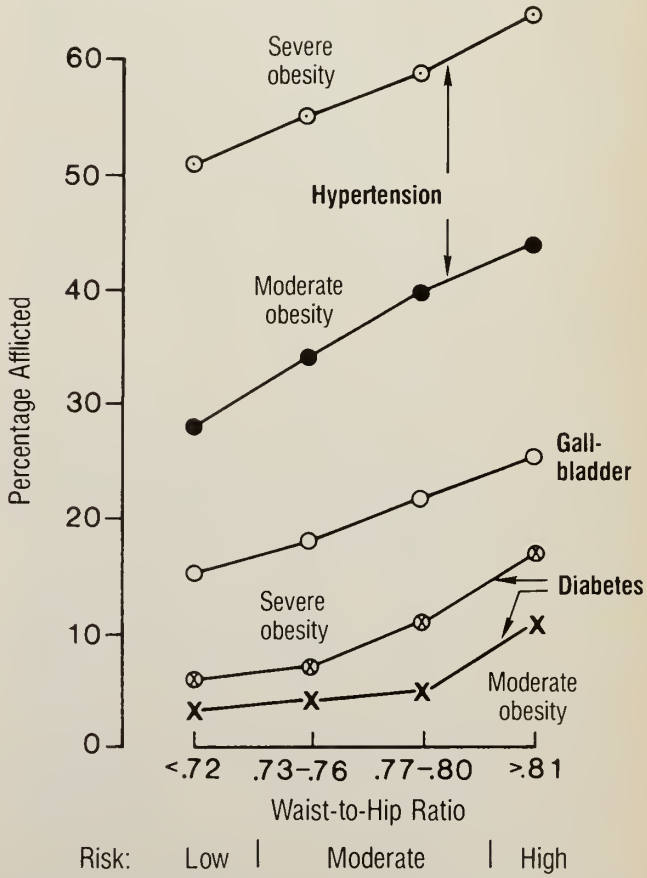

Figure 10.—These data show the relationship of abdominal (waist) to gluteal (hips) circumference ratio to various risks of obesity (from Hartz et al[59]).

sure probably results from increased peripheral arteriolar resistance. A reduction in blood pressure usually follows weight loss.[60] Obesity also increases the work of the heart, even if the blood pressure is normal. A cardiomyopathy of obesity has been reported with an associated congestive heart failure.

Diabetes mellitus. Obesity appears to stimulate the development of diabetes mellitus, and weight loss appears to reduce the risk of this disease.[61,62] Drenick followed a group of obese men, none of whom initially had diabetes.[61] During the six years of follow-up, the percentage of those with overt diabetes increased steadily to more than 40%. An additional 40% showed impaired glucose tolerance, meaning that during the six years of follow-up, more than 80% of the group showed a deterioration in glucose tolerance. The risk of diabetes is worsened with increased abdominal fat (Figure 10). With weight loss, glucose tolerance improves, insulin secretion falls, and insulin resistance is reduced.[63]

Gallbladder disease. The association of obesity with gallbladder disease has been documented in several studies.[59] Obese women between 20 and 30 years of age had a sixfold increase in the risk of gallbladder disease developing compared with normal weight women. By age 60 nearly a third of obese women can expect to have gallbladder disease.[59] The relationship to fat distribution is also evident (Figure 10). Increased cholesterol production with obesity results in increased biliary excretion of cholesterol, producing a bile that is more saturated in cholesterol, thus increasing the risk of gallstone disease in obesity.

Pulmonary function. Measurements of pulmonary function are generally normal in most obese persons.[64,65] Only with massive obesity are decreased reserve volumes and lowered arterial oxygen saturation obvious. The most important pulmonary problem in obese patients is the uncommon pickwickian or obesity-hypoventilation syndrome, which occurs mainly in the massively obese. There is a growing body of literature that suggests that the symptoms of this syndrome may result largely from sleep apnea.[64] With time, hypoxemia is followed by hypercapnia, which eventually leads to cor pulmonale.[64] Patients with the pickwickian or obesity-hypoventilation syndrome may require intensive care in a hospital to treat respiratory or cardiac failure.

Endocrine and metabolic changes. The basal concentration of growth hormone is normal or reduced in obese persons, and there is a negative correlation between body mass index and the integrated concentration of growth hormone obtained by frequent sampling over a 24-hour period.[66] The induction of hypoglycemia with insulin normally stimulates a rise in the level of growth hormone, but in obese patients this response is reduced.[5]

Nutrition appears to be more important than body weight itself in determining the circulating concentration of triiodothyronine (T_3).[67] During fasting or severe caloric restriction, total thyroxine (T_4) levels remain normal, but the serum concentration of total T_3 falls and that of reverse T_3 increases. In contrast to starvation, overnutrition is associated with a rise in serum T_3 and a fall in reverse T_3 values[67] in both obese and lean subjects.

The diurnal rhythm of cortisol is preserved in patients with simple obesity,[5,68] but the afternoon values may be above normal. There is a small, significant, negative correlation of cortisol with the percentage of overweight in women but not in men. Administering 1 mg of dexamethasone at midnight followed by measuring plasma cortisol or urinary free cortisol levels the next morning is the best screening test to separate a diagnosis of obesity from that of Cushing's syndrome. Obese patients whose cortisol levels are not suppressed with this test are a small group for whom more complex procedures are needed to exclude the possibility of Cushing's syndrome.

In obese men, the concentration of testosterone in plasma is decreased.[68] This reduction in the total testosterone level is accompanied by a reduction in the level of sex hormone-binding globin, resulting in a normal level of free testosterone in moderately obese men.[69] In massively obese men, however, there may also be a decrease in the free testosterone level as well.

In obese girls, the onset of menarche frequently occurs at a younger age than in normal weight girls.[5] The observation that menstruation is initiated when body weight reaches a critical mass provides one explanation for this phenomenon. As the rate of growth accelerates in late childhood, the entrance into this critical weight range initiates the pubertal process. Because obese girls grow faster and enter this critical mass at a younger age than normal ones, menstruation usually starts at an earlier age. Obese women often show less regularity of menstrual cycles and a greater frequency of menstrual abnormalities. In one study, 43% of 100 women with menstrual disorders were overweight.[70]

Does Weight Loss Improve Health?

Both insurance companies[43,44] and the Framingham study[71] have provided data that suggest that weight reduction may be beneficial to health. In both men and women who successfully lose and maintain a lower weight, mortality was reduced to within the normal limits based on sex and age according to life insurance statistics. Data from the Framingham study showed that a 10% reduction in relative weight for men was associated with a fall in serum glucose levels of 2.5 mg per dl, a fall in serum cholesterol levels of 11.3 mg per dl, a fall in the systolic blood pressure of 6.6 mm of mercury, and a fall in serum uric acid levels of 0.33 mg per dl.[71] For each 10% reduction in the body weight of men, these data predict that there would be an anticipated 20% decrease in the incidence of coronary artery disease.

Clinical Types of Obesity

Genetic Factors

In human obesity, genetic factors manifest themselves in two ways. First, there is a group of rare or dysmorphic forms of obesity in which genetic factors are of prime importance. Second, there is a genetic substrate upon which environmental factors interact in the development of obesity.

The dysmorphic forms of obesity are listed in Table 5, and while obesity is only of moderate degree in most, it may be pronounced in a few. These forms of obesity are transmitted by both recessive and dominant modes of inheritance. The Prader-Willi syndrome is associated in about half of persons with a translocation or a deletion of chromosome 15. For a more detailed discussion of dysmorphic obesity, the reader may consult other sources.[72]

Although studies show that obesity runs in families, they do not critically separate environmental from genetic factors.[5] This can only be done in studies of adopted children and twins. Using the Danish registry, Stunkard and colleagues examined 800 adoptees.[73] There was no relationship

between the body mass index in the adoptive parents and their children. On the other hand, the body mass index of the biologic parents increased with increasing weight of the children. These data suggest that inheritance plays an important role in the risk of obesity developing and are consistent with most studies of the adopted.[74]

The most definitive evidence for genetic versus environmental factors in obesity comes from examining body weight in twins.[75,76] Monozygotic twins have identical genetic material, whereas dizygotic twins have the genetic diversity of brothers and sisters but the closeness of monozygotic twins. Evaluating these groups of twins, along with other siblings and more distant relatives, should make it possible to separate nature from nurture. Using the body mass index as the criterion for obesity, Stunkard and associates compared 1,983 male monozygotic and 2,104 male dizygotic twins.[75] Monozygotic twins had higher correlations between body weights than the dizygotic twins, and calculations of the heritability for obesity suggested that nearly two thirds of the variation in body weight could be attributed to genetic factors.

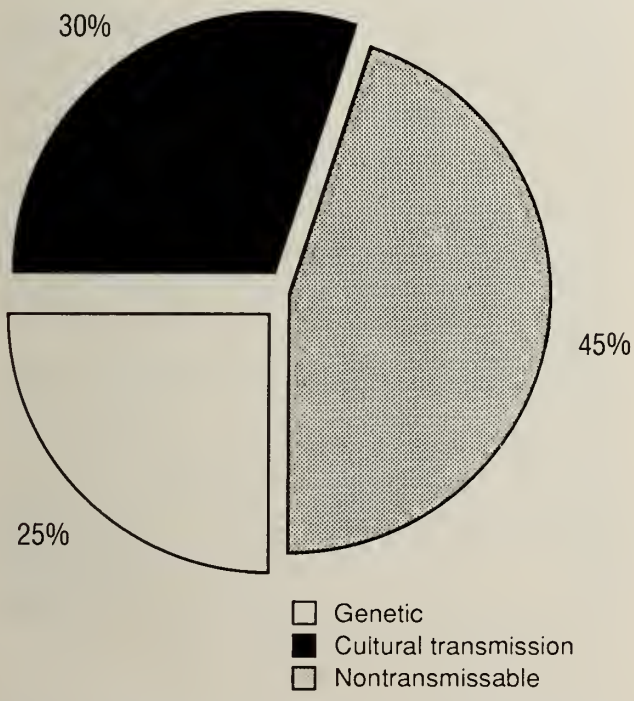

Figure 11.—The genetic and nongenetic transmission of body fat, fat mass, and extremity-to-trunk skin-fold ratio measurements are shown (from Bouchard et al[76]).

Bouchard and co-workers have examined the skin folds and total body fat in various groups with differing degrees of genetic relationships, including monozygotic and dizygotic twins.[76] Adopted siblings have a low order of correlation, but biologic siblings showed a higher one. As might be expected, this was highest among the monozygotic twins. Biologic siblings had a lower order of correlation for all of the variables than did dizygotic twins, although they all had the same genetic variation, suggesting that there was an environmental influence operative in the dizygotic twins that was absent in the biologic siblings. The genetic and nongenetic components for body fat and body mass index are shown in Figure 11.

In summary, single and polygenic inheritance are both involved in the transmission of obesity. Genetic factors may be of less importance than environmental ones in the determination of body fat and its distribution.

Classifying Obesity

Obesity can be classified in at least three ways: by the anatomic characteristics and regional distribution of adipose tissue; by etiologic causes; and by the age at onset.

Anatomic. The anatomic classification is based on the number of adipocytes. In many who become obese in childhood, the number of adipocytes may be increased twofold to fourfold. People with increased numbers of fat cells are classified as having hypercellular obesity, which is distinguished from other forms of obesity in which the total number of adipocytes remains normal but the size of individual fat cells is increased. In general, all obesity is associated with an increase in the size of adipocytes, but only selected forms have an increase in the total number of such fat cells.

Obesity may also be classified according to body fat distribution. As mentioned, both men and women with abdominal or android obesity have an increased risk of cardiovascular disease, hypertension, and diabetes. On the other hand, gluteal or gynoid obesity appears to have a much lower risk.

Etiologic. There are a number of causes of obesity. Endocrine diseases may cause obesity, but they are rare. Moreover, with endocrine diseases the increase in fat is usually

TABLE 5.—*Syndromes of Obesity, Hypogonadism, and Mental Retardation*

Syndrome	*Mental Retardation*	*Inheritance*	*Stature*	*Obesity Type and Onset*	*Craniofacial Features*	*Limbs*	*Reproductive Status*	*Other*
Prader-Willi . . .	Mild to moderate	Sporadic—2/3 have defective chromosome 15 (q:1.2)	Short	Generalized, moderate; severe; onset: 1-3 yr	Narrow bifrontal diameter, almond-shaped eyes, strabismus, V-shaped mouth, high arched palate	Small hands and feet; hypotonia	Primary hypogonadism	Enamel hypoplasia
Bardet-Biedl . . .	Mild to moderate	Autosomal recessive	Normal, infrequently short	Generalized; early onset: 1-2 yr	Not distinctive	Polydactyly	Primary hypogonadism	. . .
Alström	None	Autosomal recessive	Normal, infrequently short	Truncal; early onset: 2-5 yr	Not distinctive	No abnormalities	Hypogonadism in males only	. . .
Cohen	Mild	Probably autosomal recessive	Short or tall	Truncal; midchildhood, age 5	High nasal bridge, arched palate, open mouth, short philtrum	Hypotonia; narrow hands and feet	Normal gonadal function or hypogonadotrophic hypogonadism	. . .
Carpenter's . . .	Mild	Autosomal recessive	Normal	Truncal, gluteal	Acrocephaly, flat nasal bridge, high arched palate	Polydactyly, syndactyly, genu valgum	Secondary hypogonadism	. . .

small. Hyperinsulinism, produced by islet cell tumors or by injecting excess quantities of insulin, produces an increased food intake and increased fat storage, but the magnitude of this effect is small. A somewhat more substantial obesity occurs with the increased cortisol secretion in Cushing's syndrome. Obesity may also occur with hypothyroidism. Finally, aberrations in the distribution of body fat are also noted with hypogonadism.

Hypothalamic obesity is a rare syndrome in humans[77] but can be regularly produced in animals by an injury to the ventromedial region of the hypothalamus. This region is responsible for integrating information about energy stores and regulating the function of the autonomic nervous system. Hypothalamic obesity has been reported in humans under a variety of circumstances, the major factors being trauma, malignancy, and inflammatory disease. Symptoms and signs that accompany the syndrome include those related to changes in intracranial pressure (headache and diminished vision due to papilledema), manifestations of endocrine alterations (amenorrhea, impotence, diabetes insipidus, and thyroid or adrenal insufficiency), and a variety of neurologic and physiologic derangements (including convulsions, coma, somnolence, and hypothermia or hyperthermia). Treatment of the syndrome requires treating the underlying disease and giving appropriate endocrine support.

Physical inactivity plays an important role in the development of obesity. Gross obesity in rats can be produced by severely restricting their activity. In a modern affluent society, energy-sparing devices that reduce energy expenditure may enhance the tendency to become fat.

Diet is a third etiologic factor in obesity. This is particularly prominent in experimental animals but may also play a role in the development of obesity in humans. When rodents eat a high fat diet, drink sucrose-containing solutions, or eat a cafeteria type of diet, most strains are unable to appropriately regulate energy balance, and they ingest more energy than is needed for maintaining weight. The excess energy is accumulated as fat, and the animals become obese to varying degrees. Whether the rising fat consumption, the high intake of sugar-sweetened beverages observed in most Western nations, and the increase in corpulence in these same societies are manifestations of a similar phenomenon remains to be proved.

By age of onset. Progressive childhood obesity is a hypercellular form of obesity[5] that develops early in life; persons afflicted with this disorder show a continuing weight gain thereafter. At present, none of the forms of obesity, including progressive childhood obesity, can be detected at birth. Birth weights of children who become obese are in general not different from the birth weights of those whose childhood weights are normal. The critical periods for the appearance of progressive childhood obesity are in the first two years of life and again between ages 4 and 11. The most serious form begins in this latter period and may progress thereafter. Obesity that begins in childhood is usually hypercellular and may be resistant to therapy. Adult-onset obesity tends to be hypertrophic and features large fat cells.

The base of information about obesity has expanded dramatically in the past decade. New methods have been developed to document the degree of obesity, which have provided better evidence of the prevalence of this widespread problem. The importance of fat distribution as a risk to health has added a new dimension to the problem. It is now clear that increased abdominal fat can be as much as or more of a health risk than smoking, hypertension, or high levels of blood cholesterol. Along with this growth in knowledge has come an improved understanding of the mechanism underlying obesity. The possible roles of the sympathetic nervous system and of brown adipose tissue are two examples. The possibility that white fat cells may both increase and decrease in number during adult life needs to be reckoned with. Finally, we seem to be on the verge of new methods of treatment. The treatment of obesity will be discussed by us in the next issue of the journal.

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Medical Staff Conference

Neurologic Aspects of Cocaine Abuse

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Presenting this Medical Staff Conference, which deals with the neurologic aspects of cocaine abuse, is Michael Rowbotham, MD, Clinical Instructor of Neurology at the University of California, San Francisco (UCSF).*

In addition to his research on the psychopharmacology of cocaine in humans, Dr Rowbotham is part of the very active group in the UCSF Department of Neurology investigating the neurologic complications of cocaine use.

MICHAEL C. ROWBOTHAM, MD†: In the five years since the well-publicized death of a popular comedian and the serious injury of another, cocaine has dominated the news like few other issues. Despite a torrent of negative press on all aspects of cocaine use, the "cocaine epidemic" is far from over. In the medical literature, with every passing month come new reports of toxicity associated with its use. Fortunately, it is now widely recognized among physicians that even an occasional use of cocaine by the intranasal route can produce fatal complications. Unfortunately, despite the large volume of published medical literature on cocaine, relatively little is known about the pathophysiology of medical complications associated with its use. Even less is known about the effective prevention and treatment of cocaine-associated medical illness.

The First Wave of Cocaine Use

In the past two decades, we have seen the cyclic romance with cocaine repeated. In an identical replay of the 1880-1920 wave of cocaine use, we are now in what has been described as the third stage in the cycle of drug use in a society. First, a small elite experiments with the drug and reports few negative effects. Second, a middle period of the dispersion of drug use to a wide population and a recognition of ill effects takes place. Finally, a period of rejection ensues as the popular image of the drug becomes negative.

In 1880 an Italian neurologist, Paolo Mantegazza, waxed lyrical about the effects of cocaine on his favorite subject—himself. After describing the physiologic effects of the coca leaf in detail, he wrote: "God is unjust because He made man incapable of sustaining the effect of coca all life long."[1] A few years later Sigmund Freud began to experiment with cocaine after reading of its use in the treatment of morphine withdrawal and of battlefield exhaustion. In his famous 1884 paper, "On Coca," Freud listed many therapeutic uses for cocaine, including its local anesthetic effects. Fame for this discovery went not to Freud but rather to his two ophthalmologist friends, Carl Koller and Leopold Konigstein, who demonstrated the usefulness of cocaine as an anesthetic in eye surgery. Also in the 1880s, William Halsted began injecting cocaine into peripheral nerves to produce regional anesthesia for surgery.

Cocaine use was costly to these early researchers. Freud's career was nearly destroyed when his colleague Fleischl became cocaine-dependent in an effort to overcome morphine addiction and when one of Freud's patients died of a cocaine overdose. Halsted also became cocaine-dependent, "curing" himself by becoming morphine-dependent. By 1891, more than 200 reports of systemic cocaine intoxication had appeared, with 13 deaths attributed to the drug. Despite this, cocaine-containing patent medicines and tonics became popular, none more so than Coca-Cola and Vin Mariani.[2,3] Angelo Mariani's cocaine wine advertisements included testimonials from two popes and a host of reigning monarchs. Eventually the hazards of cocaine use were appreciated and its widespread use in the United States gradually ended following passage of the Harrison Narcotics Act in 1914.

During this same period, an understanding of the physiologic effects of cocaine progressed rapidly. Sollman's *A Manual of Pharmacology,* published in 1922, described in detail the cardiovascular, respiratory, thermoregulatory, mydriatic, and local anesthetic actions of the drug. The stimulant effects on the central nervous system and abuse liability are explained, as is the convulsive toxicity of the drug. The central nervous system effects were noted to follow a path from elation and vigor to mania and delusions, with depression following drug withdrawal.[4] In a special article in the *Journal of the American Medical Association* in 1924, Mayer reported an analysis of 43 deaths from local anesthetics, primarily cocaine.[5] Although the effect of cocaine in blocking the neuronal reuptake of norepinephrine was not to be described for another 35 years, he astutely pointed out the hazards of using cocaine and adrenaline together in anesthesia.

The Current Wave of Cocaine Use

From the latter half of the 1920s through much of the 1960s, cocaine was expensive and favored mostly by jazz musicians, members of the cultural avant-garde, and affluent drug dealers. The introduction of inexpensive synthetic am-

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
EEG = electroencephalogram
ICSS = intracranial self-stimulation
SFGH = San Francisco General Hospital and Medical Center
UCSF = University of California, San Francisco

phetamines in the 1930s reduced the popularity of cocaine to the point where only 2.8 kg (6 lb) of the drug was seized by the Federal Bureau of Narcotics in 1960. During this long period of obscurity, cocaine gained a reputation as the nonaddicting "champagne" of drugs. As recently as 1980, cocaine was claimed in major textbooks to be a relatively safe, nonaddicting euphoriant drug. The stage was set for the next wave of popularity of cocaine. By 1986, the National Institute on Drug Abuse estimated that almost 15% of the United States population had tried cocaine and that 3 million people abused cocaine regularly.[6] Although cocaine had been injected since the turn of the century, the introduction of low-priced "crack" made cocaine smoking a widespread practice. By the smoked route, extremely high blood levels can be achieved within seconds and the latency between first use and addiction shortened from years to weeks. It was estimated in 1984 that 18% of cocaine users smoked cocaine, a percentage that is likely to be higher now. With such a large number of people abusing cocaine, previously unrecognized complications began to emerge in the medical literature. The full impact of widespread cocaine smoking in the form of "crack" is not yet known, but the introduction of "crack" into the Bahamas in 1983 dramatically increased the number of persons seeking treatment for cocaine addiction and medical problems related to cocaine abuse.[7] The medical complications of cocaine have been the subject of several comprehensive reviews, but relatively little attention has been paid to the incidence, pathogenesis, or treatment of cocaine-related neurologic complications.[6,8-10]

Physiologic Effects of Cocaine Use

Although some of the medical complications of cocaine use represent a sudden expression of previously silent anatomic abnormalities that put even a first-time user at risk, most are related to compulsive high-dose cocaine abuse. Why is cocaine so addicting? To understand this, a brief review of the pharmacology and neural effects of cocaine is necessary. Cocaine is an alkaloid prepared from the leaves of the plant *Erythroxylon coca.* Cocaine hydrochloride is the water-soluble salt used medicinally. It decomposes on heating and melts at 195°C. The cocaine alkaloid, or "free base," is not soluble in water. It melts at 98°C and vaporizes at higher temperatures without decomposing, allowing it to be smoked.[8] The plasma half-life of cocaine is approximately 60 to 80 minutes, much shorter than that of methylphenidate and amphetamines.

The time course of the physiologic and subjective effects of a single dose of cocaine is closely correlated with the route of administration and blood concentrations achieved. An oral dose of 2 mg per kg body weight produces peak effects in about 45 minutes, with a rise in the heart rate of 27 beats per minute, a rise in the systolic blood pressure of 26 mm of mercury, a decrease in the skin temperature of 7°C, and a 1-mm increase in pupil size.[11] Administered intravenously, intense effects can be achieved with doses one-fifth those administered orally. When smoked, an intense and relatively brief mental and physiologic state follows just one or two inhalations of cocaine, reflecting a concentrated bolus delivered efficiently to the brain with only eight seconds of transit time.[12] An intravenous infusion of lethal doses of cocaine in dogs produces a predictable sequence of events culminating in generalized convulsions and death. The heart rate, blood pressure, cardiac output, and body temperature all rise, with the blood pH falling to nearly 7.0 as convulsions begin.[13] Rapid administration of a lethal dose can produce apnea and cardiac arrest without generalized convulsions. The experience of cocaine "body packers"—persons who smuggle cocaine by ingesting large numbers of cocaine-filled balloons or condoms—who had one or more packets rupture while in hospital has confirmed this same sequence of events in humans.[14-16] Before the onset of generalized seizures, a toxic delirium was observed.

The effects of the repetitive administration of cocaine are more complex. Tolerance to both the subjective and the cardiovascular effects of cocaine occurs quickly. Fischman and Schuster gave a group of experienced human cocaine users the opportunity to self-administer repeated bolus doses of cocaine as often as every ten minutes in a tightly controlled experimental situation.[17] Even though blood levels continued to rise throughout the experiment, the subjects could not discern any additional increase in effects after the first few doses. The same effect was observed for doses administered 60 minutes apart. Post described an orderly progression of clinical syndromes of euphoria, dysphoria, and paranoid psychosis related to the dose and chronicity of use.[18] High-dose cocaine abuse in humans produces disinhibition, impulsiveness, hypervigilance, compulsively repeated actions, and extreme psychomotor activation.

Access to the drug is a critically important factor in understanding the complications of cocaine abuse. Under proper conditions, monkeys will self-administer the same drugs taken illicitly by humans, a laboratory model used extensively in research on psychoactive drugs. Animals will self-administer cocaine under a broad range of conditions and by all routes, which may be an indication of the substantial size of the human population at risk for abuse. Cocaine has been a potent reinforcer in all animal species tested so far, evidence that a preexisting psychopathologic disorder is not a prerequisite for cocaine addiction in humans. Once self-administration has begun, the organism becomes totally preoccupied with acquiring the drug to the exclusion of food and socialization.[19] Given unlimited access, animals self-administer the drug in erratic bursts, similar to the cocaine binging seen in humans, with seizures or exhaustion terminating each binge.[20,21] In contrast, when access to cocaine is limited, animals self-administer cocaine in a relatively regular manner with greatly reduced morbidity and mortality. The economic parallel to human use patterns is unmistakable. Users report that, once started, binge use continues until no more drug is available. In the past, the high price of cocaine, difficulties in converting the hydrochloride to the free base, and the natural reluctance of most people to inject themselves provided limits on cocaine use that allowed most users to maintain health and continue to work. Longitudinal observations of cocaine users in the 1970s and early 1980s indicated about a two-year period between first use and addiction. With the introduction of cheap cocaine in the smokable base form, extremely high blood levels can be achieved almost instantaneously and maintained for longer periods,

increasing the likelihood of behavioral and medical toxicity and establishing an addictive pattern of use much more rapidly, sometimes within weeks.

Neurologic Effects

Knowledge of the neurochemical actions of cocaine has continued to advance in recent years. The local anesthetic actions of cocaine were described by Freud more than 100 years ago. As do lidocaine, procaine, and related drugs, cocaine blocks the sodium channel and inhibits the depolarizing inward sodium current necessary for impulse propagation along axons. Unlike all other local anesthetic drugs, cocaine has potent sympathomimetic actions.[22] In 1959 Trendelenburg found that cocaine inhibited the neuronal reuptake of administered catecholamines like norepinephrine and epinephrine.[23] Later, serotonin and dopamine were added to the list of transmitters whose inactivation by reuptake was blocked by cocaine. In 1978 Chiueh and Kopin showed that increased blood levels of epinephrine and norepinephrine after systemic cocaine administration were due in large part to a centrally mediated release of the transmitters from the sympathoadrenal medullary system.[24] Later work has indicated that cocaine also stimulates release of both serotonin and dopamine. Cocaine binding sites have been identified in the brain, but their density and distribution in relation to the dopamine, norepinephrine, and serotonin systems are not yet known.

Much of our knowledge about the effects of cocaine comes from comparing cocaine with other stimulant drugs and studying brain "reward" systems. Although the neurochemical basis of the euphoriant effect of any of the stimulant drugs is still not clear, it does not depend on any one neurotransmitter system.[6] This is based on a large body of research using drugs with specific neurochemical effects to try and modulate the euphoriant effects of stimulants and the observation that these more specific drugs are not euphoriants. Cross-tolerance occurs between cocaine, amphetamine, and methylphenidate in self-stimulation studies.[25] These three drugs have some neurochemical actions in common, especially dopamine release and catecholamine re-uptake blockade. Since Olds and Milner's discovery in 1954 that rats would work to earn electrical stimulation of some but not all portions of their brains,[26] intracranial self-stimulation (ICSS) had proved a powerful tool in research on stimulants. Cross-tolerance occurs between ICSS and stimulants, and procedures that alter ICSS also affect stimulant self-administration. Several lines of evidence indicate that dopamine, but not norepinephrine, is critical in maintaining the self-administration of cocaine. The mesolimbic and mesocortical dopaminergic pathways must be intact. 6-Hydroxydopamine lesions in the nucleus accumbens, medial prefrontal cortex, or the dopamine neurons of the ventral tegmental area in the brain stem disrupt cocaine self-administration. Dopamine-receptor blockers, but not noradrenergic blockers, also disrupt cocaine self-administration.[27] It has recently been shown that the self-administration of cocaine is related to its binding of neuronal dopamine transporters but not to its binding of the transporters for norepinephrine and serotonin.[28]

The long-term administration of cocaine produces supersensitivity of central dopaminergic, α-adrenergic, and β-adrenergic receptors. Brain dopamine levels and striatal tyrosine hydroxylase levels are persistently decreased in rats, and a variety of neuroendocrine changes have been noted in human cocaine abusers.[29-31] Responses to ICSS are persistently decreased, indicating a long-lasting subsensitivity of brain "reward" areas. These effects are thought to underlie the cocaine withdrawal syndrome and the persistent anhedonia seen in habitual stimulant abusers. Conditioned cues from the environment in addition to these physiologic changes may explain why relapse rates after abstinence in cocaine abusers are so high.

TABLE 1.—*Neurologic Complications of Cocaine Abuse in Adults*

Seizures	Single
	Multiple
	Status epilepticus
Stroke	Subarachnoid hemorrhage due to rupture of arteriovenous malformation or aneurysm
	Intracranial hemorrhage
	Nonhemorrhagic infarction
Headache	
Transient focal symptoms and signs	
Toxic encephalopathy	

Cocaine can produce a variety of neurologic problems, a finding that is not surprising when one keeps in mind that it is both a potent sympathomimetic and a local anesthetic agent. A short list of reported neurologic complications in adults is presented in Table 1. Of these, seizures are correlated with the route and the amount of drug used. Others, such as stroke, may be idiosyncratic reactions to the drug of unknown pathogenesis that can affect both first-time and experienced users. Preexisting anatomic abnormalities, such as coronary artery disease and cerebrovascular anomalies, may render some persons particularly likely to suffer medical catastrophes after using modest doses. The use of cocaine does not need to be active; the fetus and newborn are at special risk as well.

Cocaine-Induced Seizures

Seizures induced by cocaine were well recognized before the 1920s. The convulsant effects of cocaine are most likely related to its local anesthetic effects. Lidocaine is an anticonvulsant at low doses but is a potent convulsant at doses similar to those required to produce convulsions with cocaine. Likewise, multiple seizures following the rupture of cocaine-filled condoms in "body packers" have been associated with high blood levels of 2.0 to 5.2 μg per ml.[14,15] Comparison studies of amphetamine, cocaine, and lidocaine in seizure-kindled paradigms have shown that cocaine's effects on brain electrical activity are similar to those of lidocaine.[32] Studies by Matsuzaki and others have shown that seizure activity induced by cocaine begins in the temporal lobe and then generalizes.[33] The daily administration of a convulsive dose of cocaine produces bizarre behavior and abnormal interictal electroencephalographic activity recorded using depth electrodes, but the mean convulsive dose rises instead of falls over time. The role of catecholamines in cocaine-induced seizures is not yet clear. A nearly total selective depletion of either brain dopamine or norepinephrine has no effect on cocaine-induced seizures.[34] Pretreatment, however, with drugs that antagonize all cocaine effects and have a more general effect on catecholamines, such as chlorpromazine and reserpine, prevent cocaine-induced seizures. Of the traditional anticonvulsants, only diazepam and barbi-

TABLE 2.—*Evaluation of Suspected Cocaine-Induced Seizures**

Toxicology: urine specimen for cocaine, cocaine metabolites, and other drugs
CBC, sedimentation rate, chemistry panel, thyroid function tests, FTA test
Brain imaging: computed tomography or magnetic resonance
Lumbar puncture
Electroencephalogram

CBC=complete blood count, FTA=fluorescent treponemal antibody

*Patients with multiple observed seizures or status epilepticus require monitoring of core body temperature, cardiorespiratory function, and an electroencephalogram. See text for details.

turates have any protective effect. Phenytoin has been found to be ineffective in animals, and carbamazepine has not been adequately studied. Two factors greatly reduce the blood level of local anesthetic required for seizure production: an elevated body temperature and a decreased blood pH. In their study of cocaine poisoning in dogs, Catravas and Waters found that merely placing the animals in a cold room prevented the hyperthermia, seizures, and death produced by cocaine.[13]

The management of a patient with cocaine-induced seizures is empiric at this time and should be based on the presentation. All patients should have a thorough evaluation to rule out other causes of seizures. A schema for evaluation is shown in Table 2. If no cause for a seizure other than drug use is found, no long-term treatment other than drug abstinence is required because of both the lack of effect of traditional anticonvulsants in preventing cocaine-induced seizures and the lack of evidence that cocaine-induced seizures will later produce seizures independent of usage of the drug. A patient who presents with a history of a single, unobserved seizure related to cocaine use and is not cocaine intoxicated at the time of presentation should be evaluated for a nondrug cause of the seizure but will not require immediate anticonvulsant therapy. The electroencephalogram (EEG) should be normal soon after the seizure. A patient who presents with a history of cocaine-induced seizures and is intoxicated with the drug or who has an observed seizure in the emergency department requires a rapid and thorough assessment. Attention to the basics—blood pH, core body temperature, and electrocardiogram—is the first step. A urine specimen should be sent for a toxicologic analysis. Once the patient is stable, brain imaging with computed tomography (CT) or magnetic resonance imaging followed by lumbar puncture should be carried out to exclude stroke, subarachnoid hemorrhage, and infection. An EEG and other studies will be necessary to rule out other causes of seizures. If only a single seizure occurs and the patient recovers rapidly, no anticonvulsants are needed. If a second seizure is observed, diazepam can be administered to stop the seizure, but phenytoin loading should be carried out without delay. Although the use of phenytoin may not be effective in patients with cocaine-induced seizures, a reliable history and toxicologic confirmation are not available in the emergency situation, and a standard treatment protocol should be followed.

If status epilepticus develops, phenobarbital loading and the protocol for pentobarbital anesthesia in use at the San Francisco General Hospital and Medical Center (SFGH) should be followed.[35] This will require admission to an intensive care unit, intubation, and continuous EEG monitoring. It is absolutely essential to keep the body temperature as near normal as possible. Not only is hyperthermia directly damaging to the brain, but there is evidence that anticonvulsants administered in this situation will be more effective if the body temperature is kept normal.[36] It is difficult to give recommendations regarding blood pH during cocaine-induced status epilepticus. The degree of arterial blood pH depression due to the lactic acidosis of seizures is not correlated with mortality or central nervous system injury.[37] Acidosis may, however, exacerbate local anesthetic-induced seizures, and cocaine may cause acidosis even before seizure activity begins. Even profound degrees of lactic acidosis are reversed by the metabolism of lactate in about an hour, and cocaine itself has a short half-life of 60 to 80 minutes. Until further research clarifies this aspect of the management of cocaine-induced seizures, attempts to correct the blood pH should not divert attention from more critical aspects of seizure control. Because cocaine-induced seizures, especially status epilepticus, are associated with high blood concentrations of the drug, arrhythmias and hypotension may coexist. I recommend avoiding using lidocaine in this situation because its similarities to cocaine may aggravate the seizures.

Drug-induced seizures are difficult to manage. When combined with hypotension and hyperthermia, morbidity and mortality are high. An illustrative case is presented in Figure 1. Assuming the patient survives, long-term anticonvulsant therapy is probably not necessary unless focal brain injury or a persistently abnormal EEG is present.

Cocaine-Induced Stroke

Stroke associated with cocaine use is a recently recognized phenomenon. There has been little research into this problem, and the literature consists almost entirely of case reports. Since the first well-described case in 1977, there have appeared 15 more articles describing a wide variety of stroke types in a total of 41 patients.[38-49] Subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke located in all vascular territories including the anterior spinal artery have now been described. Nearly all were in patients younger than 50 years and many younger than 30. Cocaine was used by the intranasal, intravenous, intramuscular, and smoked routes. The quality of the evaluations has varied widely. The first case reported by Brust and Richter was based on a clinical examination without CT confirmation.[38] Many subsequent cases reported have been limited by a lack of toxicologic confirmation of cocaine use and evaluations lacking angiography and lumbar puncture. In nine of the reported cases, angiography has documented either an arteriovenous malformation or an aneurysm. In only five cases has angiography been carried out and found to be normal. Several cases of documented middle cerebral artery branch occlusions have been associated with "crack" smoking. It is tempting to speculate about a cause-and-effect relationship between the high cocaine blood concentrations achieved nearly instantaneously by cocaine smoking and stroke of this type, but so far no evidence has emerged of a relationship between the route of administration of cocaine and the stroke type.[42] One case of "vasculitis" associated with the use of cocaine, analogous to the cerebral "speed arteritis" associated with amphetamine use, has been reported.[46] In this case, however, the spinal fluid was bloody, which alone could account for the angiographic findings.[47] Stroke may follow cocaine use within a period of seconds to as long as 12 hours. There is no ready explanation for a modest delay in the start

of the symptoms, but it indicates that stroke following cocaine use may be only indirectly related to the route, dose, and peak blood levels achieved in some cases.

Stroke in young adults is uncommon. In persons younger than 30 years, atherosclerosis is unlikely to play a role, and an underlying cause is present in most cases. In Bogousslavsky and Regli's recent series, the most important etiologic factors were mitral valve prolapse, arterial dissection, vasculitis, migraine, hypercholesterolemia, and oral contraceptive use.[50] The mechanism by which cocaine causes stroke is unknown, but it is most likely related to its sympathomimetic effects. Large doses of local anesthetic drugs like lidocaine have been used for various problems for more than 50 years without an observed relationship to stroke. In contrast, amphetamines, methylphenidate, phencyclidine, LSD, and phenylpropanolamine all share with cocaine the ability to alter vascular tone and all have been associated with stroke.[49] LSD and phencyclidine produce a potent contractile response when applied to isolated canine basilar and middle cerebral arteries that may be mediated by serotonin. The others have prominent catecholaminergic effects or directly stimulate α-adrenergic receptors. Edvinsson and co-workers showed in the middle cerebral artery of cats that cocaine produced a prejunctional type of sensitivity to norepinephrine that was similar to that produced by surgical sympathectomy.[51] The role of platelets in cocaine-associated stroke is unclear but potentially important. Catecholamines and sympathetic stimulation enhance platelet aggregation, and platelet thrombi have been found in some cases of cocaine-associated myocardial infarction. As the cerebral vasculature has not been studied pathologically in any reported case of cocaine-associated stroke, a discussion of the pathogenesis must remain speculative.

A patient with a suspected cocaine-associated stroke should have a thorough evaluation to exclude all possible treatable causes of stroke. An evaluation scheme is shown in Table 3. In addition to a toxicologic confirmation of cocaine use, brain imaging using magnetic resonance or CT, lumbar puncture, echocardiography, angiography, and hematologic studies are indicated. In the absence of an identified cause other than cocaine use, conservative treatment is advised. There is no literature to support the long-term use of prednisone, heparin, or aspirin in these cases.

Both headache and a variety of transient neurologic signs and symptoms have been observed in association with cocaine abuse.[43] Although cocaine-related headache is an uncommon reason for patients to present to an emergency department for treatment, it is a symptom commonly reported in community treatment facilities and in users calling a toll-free telephone help line. A large number of drugs have been reported to cause headaches, and headache is a common symptom in drug-withdrawal syndromes. Because of the association between cocaine and stroke and the hypertensive effects of the drug, headache is a symptom that should be taken seriously. Deciding which patients require evaluation is difficult, but a complete evaluation should include brain imaging, lumbar puncture, and, in many cases, angiography.

Sympathomimetic drugs and local anesthetics can produce transient neurologic signs and symptoms related to the amount used. The enhancement of physiologic tremor, vertigo, nonspecific dizziness, blurred vision, ataxia, and tinnitus have all been reported. Cocaine "hallucinations" drawn by users bear a notable resemblance to the visual auras of migraine. Although some symptoms may reflect an increased awareness of bodily sensations or a misinterpretation of the cardiovascular effects of the drug, focal abnormalities such as a transient hemiparesis have been seen and are of unknown origin. In animals, high doses of cocaine produce abnormal motor activity and stereotypic behavior. In humans, tics and choreiform movements due to amphetamine abuse have been noted but have not been reported in association with cocaine use. In all cases of neurologic signs and symptoms due to cocaine abuse, toxicologic confirmation of

TABLE 3.—*Evaluation of Suspected Cocaine-Associated Stroke*

Toxicology: urine specimen for cocaine, cocaine metabolites, and other drugs
CBC, sedimentation rate, ANA, chemistry panel, FTA test, coagulation studies
Electrocardiogram
Brain imaging: computed tomography or magnetic resonance
Lumbar puncture—including VDRL
4-Vessel cerebral angiography
2-Dimensional echocardiography

ANA=antinuclear antibody, CBC=complete blood count, FTA=fluorescent treponemal antibody

Figure 1.—The scans show cerebral atrophy following oral cocaine-induced status epilepticus. A 24-year-old man was brought to an emergency department in a confused and hypervigilant state. When generalized seizures began, his blood pressure dropped from 210/138 mm of mercury to 68/24 mm of mercury with a wide QRS complex tachycardia on an electrocardiogram. A blood pH of 6.77 and a temperature of 40.5°C (105°F) were noted during the ictus. Seizures continued despite intubation and the intravenous administration of diazepam, phenytoin, and phenobarbital. The blood cocaine value was 4.0 μg per ml. A noncontrast computed tomographic (CT) scan on the day of admission **(left panel)** was normal. A CT scan at 30 days **(right panel)** and thereafter showed widespread cerebral atrophy. Severe neurologic impairment was permanent.

cocaine use and the exclusion of the use of other drugs are essential. There is not yet enough information available to know which patients require a complete evaluation, but, at a minimum, all patients with abnormalities on a neurologic examination require a neurologic consultation and further study as indicated. Any patient who presents with a stroke-like syndrome following cocaine use should be promptly studied using the schema in Table 3.

Cocaine-associated behavioral abnormalities, especially a drug-induced psychosis, are commonly seen. An uncommon event is a true toxic encephalopathy following cocaine use that may present as coma of an unknown cause. This is a major medical emergency and when due to cocaine probably indicates the intake of a lethal or near-lethal dose. In addition to other evaluations and treatment indicated in managing such patients, a urine specimen for toxicology and a blood specimen for a plasma cocaine level (where available), an emergency portable EEG to exclude status epilepticus, and attention to the core body temperature are particularly important. A search of the oropharynx and x-ray films of the abdomen are needed to exclude retained cocaine-containing packets. β-Blockers such as propranolol hydrochloride are not useful in this situation. Preliminary studies in animals indicate that neuroleptics and calcium channel blockers each enhance survival in cocaine poisoning.[13,52] In humans, calcium channel blockers antagonize some effects of cocaine.[53] It must be pointed out that in these studies, the drugs were either given concurrently or as a pretreatment. Their usefulness in reversing signs of cocaine poisoning in humans remains to be proved.

Perinatal Effects of Cocaine Use

In the past three years there has been a tremendous surge of interest in complications of pregnancy and childbirth due to maternal cocaine abuse. Long-term follow-up studies are underway, but preliminary data indicate that some cognitive-behavioral abnormalities persist in the children for at least six months to two years. Even when compared with pregnant women who abuse heroin or are on methadone maintenance therapy, cocaine-using women have worse pregnancy outcomes. Increased incidences of spontaneous abortion, abruptio placentae, fetal death, and premature and precipitous labor have all been documented in these women compared with methadone-maintained and non-drug-using women.[54,55] Infants born to cocaine-using mothers are more likely to be small for gestational age and have smaller head circumferences. There have been several reports—including one prospective study—of an increased incidence of sudden infant death syndrome in infants of cocaine-using mothers, but whether the increased incidence is greater than that associated with the abuse of opiates is not established.[56,57] Perinatal cerebral infarction and hemorrhage, sometimes presenting as seizures, has occurred in full-term infants. An illustrative case is presented in Figure 2.

A variety of lesions have been seen, including diffuse atrophy, deep brain cysts, periventricular leukomalacia, and hemorrhages in many locations.[58,59] The pathophysiology of these complications received little study until recently. Woods and associates showed in pregnant ewes that the maternal administration of cocaine produced a substantial dose-dependent increase in uterine vascular resistance, an increased maternal blood pressure, and decreased uterine blood flow.[60] Associated with this were fetal hypoxemia, hypertension, and tachycardia. Directly administering cocaine to the fetus did not cause fetal hypoxemia and produced a lesser degree of hypertension and tachycardia. Of importance is that the doses used overlapped with those used experimentally in nonpregnant human volunteers and are probably similar to those used by cocaine abusers. In addition, pregnant women and infants do not metabolize cocaine as rapidly because of lower levels of plasma cholinesterases. An alternative pathway that generates the biologically active metabolite, norcocaine, may assume more importance. Urine specimens from newborns of cocaine-using mothers may test positive for cocaine metabolites for as long as five days, and cocaine exposure of the infant may continue after birth through breast milk. These findings raise the possibility that some signs, especially seizures, of the "cocaine withdrawal" syndrome seen immediately postpartum may actually represent prolonged intoxication with the drug.

The magnitude of the problem of cocaine-related neurologic illness is unknown. No population-based studies are available to estimate how frequently any of the reported medical complications of cocaine occur. A seven-year retrospective study of patients presenting for treatment for cocaine-related neurologic and psychiatric problems at SFGH was recently reported.[43] Of 989 cases attributed to cocaine use alone, 150 patients had primarily neurologic complaints. The two largest categories were seizures and focal neurologic symptoms and signs—including stroke—with headache, a transient loss of consciousness, tremor, and toxic encephalopathy occurring less frequently. The neurologic complications observed were not benign. Of the patients presenting with seizures, status epilepticus developed in two requiring pentobarbital anesthesia for control, with one patient dying and the other left with permanent neurologic sequelae. Of the patients with stroke, all had significant per-

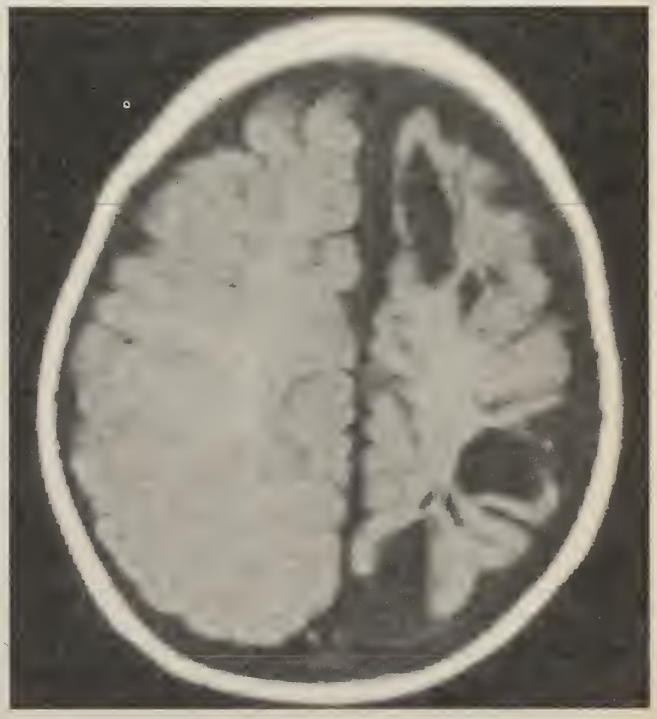

Figure 2.—Magnetic resonance imaging (MRI) of the brain of a 4-month old male infant shows multiple areas of left (viewer's right) hemispheric infarction. The mother had used cocaine but no other drugs throughout pregnancy. Seizures developed after delivery and MRI on day 4 of life showed left hemispheric edema.

manent residual effects. One of three patients admitted for toxic encephalopathy died shortly after admission with hyperthermia, rhabdomyolosis, disseminated intravascular coagulation, and renal and cardiac failure.

Consistent with nationwide trends, the number of cocaine-associated neurologic complications rose steadily each year throughout the seven-year study period. Although the number of patients seems small compared with the total number of patients seen each year at a large urban hospital like SFGH—80,000 emergency department visits and 18,000 hospital admissions annually—the problems encountered are sufficiently rare and the evidence in favor of an association with cocaine use too strong to dismiss the findings as coincidental. Population-based figures cannot be calculated, but at the present time stimulant abuse is a significant cause of stroke in patients younger than 40 years at SFGH. Cocaine abuse among pregnant women has risen considerably in recent years, and neurologic complications in newborns are frequently seen. In 1987 at SFGH, 119 mother-infant pairs tested positive for cocaine only, making up 12% of all newborns at that center.

Perhaps because of the current negative image of cocaine, the number of first-time users of cocaine has begun to decline. It will be some time before the end of the "cocaine epidemic." Another cycle of abuse of stimulant drugs will undoubtedly begin in the not-so-distant future. Next time, let us hope we more critically evaluate abuse liability and toxicity before public use spins out of control.

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Epitomes
Important Advances in Clinical Medicine

Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in pediatrics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Ribavirin and Respiratory Syncytial Virus Infections

RESPIRATORY SYNCYTIAL VIRUS (RSV) is the most frequent cause of hospital admissions of infants with respiratory tract disease. In previously healthy infants, the RSV infection subsides in three to seven days, and most infants recover without sequelae; some will have reactive airway disease with subsequent respiratory tract infections. Substantial morbidity and, infrequently, death may occur among infants with preexisting severe pulmonary or cardiac disease. Most severely affected infants have signs and symptoms of bronchiolitis or acute pneumonitis, or both, and clinically significant hypoxemia develops due to bronchiolar spasm or alveolar-capillary block, or both. A significant proportion of the sickest infants require ventilatory support. In those infants with severe bronchopulmonary dysplasia, severe cyanotic heart disease with increased pulmonary blood flow, and cellular immunodeficiency syndromes, the outcome may be uncertain.

RSV infection is generally limited to the respiratory tract epithelium; the pathogenesis of the disease probably is an extensive cellular pathologic disorder and acute host-mediated responses, including immunoglobulin (Ig) E-mediated activity. Ribavirin aerosol therapy, developed over the past decade, appears to ameliorate or diminish these pathologic events.

Ribavirin (Virazole) is a nucleoside analogue that is activated in host tissues to its phosphorylated form; antiviral activity results in the inhibition of viral RNA synthesis. Ribavirin aerosol therapy was pioneered in controlled studies among college students with acute influenza virus A infections and then extended to RSV infections among infants. Therapeutic efficacy has been shown among infants and children admitted to hospital with and without preexisting pulmonary and cardiac disease. Benefits occur without significant drug toxicity, and five-year follow-up evaluations show no effects of the aerosol therapy on the respiratory tract.

High concentrations of ribavirin are delivered in an aerosol by a small-particle aerosol generator through a mask, tent, or endotracheal tube over a 12- to 18-hour treatment period per day for three to five days or, in some cases, longer. The respiratory staff needs to give careful attention to drug precipitation in the respiratory equipment during therapy, especially among patients with endotracheal tubes in place.

In general, ribavirin therapy may be expected to control chronic infections among immunocompromised patients and to ameliorate infections among other treated inpatients. The most significant result of therapy is the relief of hypoxemia; this may be due to the control of the virus infection, an inhibition of IgE-mediated responses by ribavirin, or both. Ribavirin aerosol therapy may be indicated in infants and young children with RSV infection complicated by pneumonia, apnea, progressive bronchiolitis with hypoxemia, congenital heart disease, and chronic lung disease.

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Update on α-Fetoprotein Screening

SCREENING OF ALL PREGNANCIES for neural tube and other birth defects, using the maternal serum α-fetoprotein (AFP) level, is now a routine practice.

AFP produced by the fetal liver appears in the maternal serum in a measurable quantity by the 15th completed week and increases in concentration until term. Maternal serum AFP results are reported as multiples of the median value for a given gestational age and, as such, have provided a number of insights into conditions affecting a fetus or pregnancy.

The usefulness of maternal serum AFP screening is improved with accurate pregnancy dating and when raw values are adjusted for race, body weight, and the presence of insulin-dependent diabetes. The AFP levels can be raised or lowered in maternal serum by several conditions affecting fetal production or transplacental or amniotic diffusion. These conditions include multiple gestations; fetal demise; and structural fetal defects such as open spina bifida, gastroschisis, and omphalocele. It is necessary, therefore, to examine carefully the pregnancies of women having abnormal AFP values. This begins with ultrasonography to confirm the gestational age and the presence of a single fetus that is viable and has no structural defect. A woman with an abnormal

elevation unexplained by ultrasonography should have a specimen of amniotic fluid collected for karyotyping and AFP determination. If the AFP level is elevated, the acetylcholinesterase, an enzyme specific for neural tissue, is assayed. An elevation supports a diagnosis of open spina bifida.

The test should be done at a university or a referral laboratory with a large enough volume and experience to guarantee an accurate analysis and interpretation. The test is available in most states. California has pioneered and administered a statewide program that has screened more than 500,000 women. This program has proved to be cost-effective. The cost of care saved by termination or early treatment is about twice the cost of detection. Following this protocol, approximately 95% of anencephalic fetuses, 80% of those with open spina bifida, and many fetuses with ventral wall defects could be detected prenatally.

For several years women older than 35 years at term have been offered an amniocentesis for the prenatal detection of Down's syndrome. Because fetuses with the Down syndrome usually produce less AFP, low maternal serum AFP levels can now be used in women younger than 35 to identify an additional group of trisomic fetuses. The combination of maternal age and serum AFP levels in multiples of the median can be used to assign specific risk figures. Women with a risk equivalent to 35 years should be offered an amniocentesis. About 15% to 20% of cases of Down's syndrome are detectable by this method.

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Wald NJ, Cuckle HS: Recent advances in screening for neural tube defects and Down's syndrome. Balliere's Clin Obstet Gynaecol 1987; 1:649-676

Varicella Vaccine Update

THE FIRST REPORT OF VARICELLA VACCINE appeared in *The Lancet* a decade and a half ago. Since that time the vaccine has been licensed for use in Japan and in Europe. In the United States, the vaccine has been evaluated in thousands of normal children and in hundreds of normal adults and children with leukemia. Why has the vaccine not been licensed in this country? Varicella vaccine has been shown to confer good protection in healthy children and to modify or prevent disease in adults and in children with leukemia. In the latter groups, its use certainly reduces the morbidity that varicella is known to produce in these persons. In children with leukemia, there have been some reactions to the vaccine that are difficult to predict. In healthy children the vaccine is safe.

The main concern appears to be about the long-term effects of immunization: whether the vaccine will result in more or less zoster than in patients with natural infection. Studies in children with leukemia, however, do not suggest that there is increased risk, and, indeed, zoster may be less frequent in vaccinees. Another concern is whether the widespread use of the vaccine will result in a greater frequency of adult cases of varicella. This might occur if vaccine-induced immunity wanes or if the epidemiology of varicella is changed by reducing the opportunities for natural infection in those children who are not immunized. By combining the varicella vaccine with a vaccine that is given to virtually all children, such as the measles, mumps, and rubella vaccine, the latter concern can be assuaged. This combination has been shown to be safe and effective.

It is unlikely that we will have additional answers to these possible problems by more testing. A decision on licensure is probably at hand.

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Pediatric Physical Assessment of Sexual Abuse

CHILD SEXUAL ABUSE has been increasingly recognized in recent years. While physicians are sensitive to the psychological and social aspects of the medical evaluation, they need to be aware of the medical findings on physical examination associated with genital trauma and to understand the significance of sexually transmitted diseases in prepubescent children.

There is normal variation in the anatomy of the anogenital area of prepubescent children. Not all changes in the genital area are due to sexual abuse.

In general, the genital area of a prepubescent girl contains thin, fine structures that are scarred as a result of certain types of injuries. Not all forms of sexual abuse result in observable findings. Oral-genital contact and gentle fondling, for example, may result in no changes. External rubbing, also called vulvar coitus or dry intercourse, characteristically results in changes in the area of the posterior fourchette and occasionally hyperpigmentation of the labia majora. Actual penetration with either finger, penis, or foreign object will usually lead to disruptions in the configuration of the hymen. With a single isolated episode, the initial signs of trauma may heal within one to two weeks, and there may be minimal residual findings. With repeated episodes, the traumatized area may not have sufficient opportunity to heal, and greater changes are noted. In summary, the changes noted with repeated vaginal penetration are a reduced hymenal remnant; irregularities in the hymenal contour representing healed tears; rounding and thickening of the hymen; missing portions of the hymen; and a gaping, patulous introitus. There has been controversy concerning the size of the hymenal orifice as an indication of sexual abuse. In general, the orifice is 3 to 4 mm in girls younger than 5 years and up to 5 to 6 mm in girls between 5 and 10 years old. There is no consensus about these measurements, however, and the finding of an enlarged orifice without other changes may not be diagnostic of abuse.

Repeated penetration of the anus may lead to physical findings in only 50% of victims. Scarring, thickening, and hyperpigmentation of the perianal skin; a diminution in the number of rugae; a loss of tone; and a loss of subcutaneous supporting tissue may be present.

The presence of a sexually transmitted disease also supports the diagnosis of sexual abuse. These diseases include gonorrhea, *Chlamydia, Trichomonas,* syphilis, condylomata acuminata, and herpes simplex type 2. The presence of any of these diseases warrants further medical and psychosocial evaluation.

Referral centers with expertise in pediatric sexual abuse

may assist a clinician through experienced interviewers and with the aid of colposcopy, which provides magnification for a visual examination of the injured genital tissue.

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Jaundice in Healthy Newborns—Redefining Physiologic Jaundice

BECAUSE CLINICAL JAUNDICE becomes apparent at serum bilirubin levels of about 5 mg per dl, about 65% of all normal newborn infants appear jaundiced during the first week of life. Although the overwhelming majority of these infants are healthy, the presence of jaundice engenders anxiety in parents and physicians alike, and the management of what in most cases is a "nondisease" is emotionally and financially draining. Most pediatricians follow the advice of standard pediatric texts and do diagnostic investigations to rule out "pathologic" jaundice whenever the bilirubin level exceeds 12 to 12.9 mg per dl.

We studied 2,416 infants admitted consecutively to a well-baby nursery and found that the maximal serum bilirubin concentration exceeded 12.9 mg per dl in 147 infants (6.1%). Jaundice was associated strongly with breast-feeding ($P=.0001$) and the percentage of weight loss after birth ($P=.0001$) as well as maternal diabetes, Asian race, decreased gestational age, male sex, bruising, and the induction of labor with oxytocin. Using logistic regression analysis, we calculated the risk of jaundice for infants with or without these "icterogenic" factors. These calculations permit pediatricians to predict the likelihood of jaundice developing in a particular infant. When many risk factors are present, there is a high probability of jaundice, and, provided the baby is otherwise healthy, it is probably unnecessary, almost always unrewarding, and certainly expensive to do a battery of laboratory tests. On the other hand, we should be wary of a modestly elevated serum bilirubin level in an infant with jaundice who has few or no icterogenic risk factors. This might require further investigation.

Based on the method of feeding alone, the 95th percentile for the maximal serum bilirubin concentration in breast-fed infants is 14.5 mg per dl, whereas it is only 11.4 mg per dl for bottle-fed infants. All other factors being equal, therefore, it should not be necessary to investigate a case of a jaundiced, healthy, breast-fed infant unless the serum bilirubin level exceeds about 15 mg per dl, whereas in a bottle-fed infant such investigations may be indicated if the serum bilirubin level exceeds about 12 mg per dl. Including the other risk factors mentioned above further refines this approach. We need a new definition of what is, and what is not, physiologic jaundice.

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AIDS in Schools and Day-Care Centers

AMERICAN CHILDREN younger than 13 years diagnosed with the acquired immunodeficiency syndrome (AIDS) numbered 934 by April 1988. The estimated number of cases in 1991 is 3,000. Many children with AIDS are well enough to benefit from the developmental and educational opportunities of day-care attendance and elementary school education. In addition to the number of children with AIDS are children with the AIDS-related complex and those without symptoms but who are seropositive for antibodies to the human immunodeficiency virus (HIV). Children acquiring HIV in the perinatal period are asymptomatic for an average of six to eight months. Those who acquired the infection before 1985 from a transfusion of blood or blood products have had a mean incubation period of two years. Some have remained asymptomatic for as long as seven years.

The enrollment of these children in child-care settings and elementary schools has raised concern among those providing these services. Child-care and school issues requiring physicians' responses include the communicability of HIV to healthy children and staff, mandatory serologic screening, the potential for secondary infections in children with AIDS, and conflicting obligations to protect privacy and to inform.

Responses to such concerns are based on the current understanding of HIV communicability. The nonsexual household transmission of HIV is rare; the few reported cases involve extraordinary circumstances and poor adherence to hygienic precautions. Not one case of HIV infection has been transmitted in a school or day-care setting. Although HIV has been identified in saliva, tears, and urine, there is no evidence that these fluids are involved in the transmission of the infection.

Casual contact as would occur among children in an elementary school should not be considered a risk for the communicability of HIV. The benefits of unrestricted school attendance to most school-aged children seropositive for HIV outweigh any remote risk of viral transmission. HIV-seropositive infants, toddlers, and older children with subnormal development are more likely to lack control of their body secretions and to practice frequent hand- and object-mouthing behaviors and biting behaviors. These children and HIV-seropositive children with oozing skin lesions hypothetically pose an increased risk to others. For these cases, exclusion from a group program should be decided on a case-by-case basis by qualified persons including the child's physician and a person familiar with the educational setting.

Hygienic practices in day-care centers and schools can contain the spread of infectious diseases and are recommended in the presence or absence of known HIV-infected persons. Child-care personnel and educators can minimize their exposure to HIV by carefully attending to hand washing. In regions with a high prevalence of HIV infection, consideration should be given to protecting open skin lesions and dry, cracked skin with disposable gloves when handling body fluids and excrement. Caution in disposing of soiled towels, diapers, and sanitary napkins must become routine. Soiled surfaces and mops should be cleaned with disinfectants (household bleach diluted 1:10 with water).

Mandatory screening for HIV as a condition for school or day-care enrollment is unwarranted. A physician, not the educational facility, should be responsible for assessing the risk of secondary infection to an HIV-positive child who may be immunosuppressed. Notifying school personnel of a

child's HIV status would expedite preventive action by the parent or physician of an immunocompromised HIV-positive student when there is a school epidemic. The cost of even limited disclosure, however, will often be the needless ostracism of the child from school. Information about a child's immunodeficiency, regardless of its cause, should be disclosed to certain care givers, but a child's HIV-seropositive status is to remain confidential information. Exceptions may be to inform those staff members who directly care for children with frequent biting behavior or children incapable of controlling body secretions.

The responsibility of the schools goes beyond safely enrolling HIV-seropositive children in their classrooms. Given that vaccine development is not imminent, community education is the most efficient means of controlling the spread of HIV, and schools have the capability and responsibility to provide this education. Guidelines for an educational curriculum directed towards various grade levels are available from the Centers for Disease Control to educators who want an effective strategy to teach students how to avoid HIV infection.

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Management and Ethical Dilemmas of Diagnosing and Treating Fetal Heart Disease

MAJOR ADVANCES IN ULTRASOUND IMAGING over the past ten years currently provide a systematic approach to evaluating the anatomy, physiology, and rhythm of the fetal heart, with detailed imaging available as early as the 14th to the 15th week of pregnancy. Pediatric cardiologists, perinatologists, and radiologists, often working together, have diagnosed almost every major form of congenital heart disease correctly before birth. Such notable success has not come easily, and, in general, physicians working in this area have often required two to five years of extensive experience to achieve proficiency using ultrasound for a detailed cardiovascular evaluation before birth.

Indications for fetal cardiac ultrasonography include maternal diabetes, maternal drug exposure, maternal infection, a family history of congenital heart disease in a parent or sibling, or persistent fetal arrhythmia. The largest "pick-up" rate for major forms of congenital heart disease will occur if obstetricians evaluate a four-chamber cardiac view as a part of their routine obstetric ultrasonographic screening procedure. They should see the atrial and ventricular septa and four chambers relatively symmetrically dividing the cardiac ultrasound "silhouette" in this plane. Perhaps 90% of the major forms of congenital heart disease can be ruled out by a normal four-chamber view.

Alternatives available in the aftermath of the diagnosis of congenital heart abnormality may include pharmacologic therapy for an arrhythmia; counseling a family about the natural history—catheterizations, heart operations, and the like—of infants with similar forms of congenital heart disease after birth; and counseling related to terminating a pregnancy in the appropriate circumstance or making arrangements for the timing and method of delivery for the appropriate medical or surgical intervention after birth, including consideration of a neonatal heart transplantation for certain inoperable conditions. Major additional capabilities for evaluating the fetal heart have arisen with the application of the Doppler to evaluate cardiac function in cases of valvular disease, and high-resolution color flow mapping has assisted in evaluating septal defects as well as the aortic arch and conal truncal abnormalities.

The field of fetal cardiology is rapidly advancing. It requires the highest level of technical skills and cooperation among obstetric, pediatric, neonatal, ethical, legal, genetic, and surgical colleagues. Several tertiary hospitals have developed centers for fetal diagnosis and treatment where such multidisciplinary expertise can be coordinated, not only for cardiac but for other organ system diseases diagnosed and potentially treated in the fetal stage. Through regionalized team efforts, advances in this dynamic area of fetal medicine will be controlled and yet nurtured to encourage further advances.

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Exogenous Surfactant for the Respiratory Distress Syndrome

SINCE THE 1970s, therapy for the neonatal respiratory distress syndrome has focused on metabolic resuscitation and assisted ventilation of preterm infants with ventilatory failure until the gene controlling surfactant production and secretion is activated. Surfactant deficiency is central to the pathophysiology of the respiratory distress syndrome. Successful exogenous surfactant administration has led to the development of several promising surfactants for exogenous use.

Human surfactant, derived from amniotic fluid, contains all surfactant proteins (SP-A, -B, and -C), phospholipids identical to "mature" adult surfactant, and a small percentage of neutral lipids. Human surfactant instilled into the airways has been shown to reverse ventilatory failure from the respiratory distress syndrome; to bring about a rapid improvement in oxygenation; and, in very premature infants, to decrease the mortality and the prevalence of bronchopulmonary dysplasia.

Several "first-generation" surfactants have shown promise in clinical trials. Surfactant TA, calf lung surfactant extract, and human surfactant are currently being evaluated in multidose clinical trials to establish efficacy and safety. Synthetic surfactant, not derived from natural sources and

void of surfactant protein (Exosurf), is concurrently being studied in similar trials. Both preventilatory treatment and postventilatory "rescue" trials of surfactant treatments are being systematically investigated using these surfactants. Using human surfactant has thus far been free of complications, and the two-year neurodevelopmental follow-up evaluation suggests an overall improvement in treated infants.

Critical advances in isolating surfactant components and cloning suggest that recombinant surfactants, comprising critical proteins or biologically active peptides and phospholipid mixtures in ideal combinations, will become "second-generation" surfactants.

Until the efforts of genetic engineering are successful, neonatologists will be limited to using natural surfactant derivatives or artificial surfactants in carefully controlled trials sanctioned by the Food and Drug Administration. Of course, only premature infants with evidence of surfactant deficiency should receive this experimental therapy. If the present trials are successful, surfactant therapy should by 1990 become a mainstay of the treatment of the respiratory distress syndrome.

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Bronchopulmonary Dysplasia (Infantile Chronic Lung Disease)

WITH THE INCREASED SURVIVAL of neonates who have severe respiratory insufficiency, bronchopulmonary dysplasia has become an important cause of chronic illness during the first five years of life. Causes of respiratory tract injury in early infancy that may lead to bronchopulmonary dysplasia include lung immaturity (hyaline membrane disease); aspiration syndromes; infection, especially viral; and respiratory tract malformations associated with impaired mucociliary function and chronic airways soilage. These infants survive with impaired mucociliary clearance mechanisms, increased bronchial reactivity and bronchomotor tone, and impaired lung water dynamics.

While diuretic and bronchodilator therapy continue to be mainstays of management, recent studies have shown the importance of adequate oxygenation for the recovery from bronchopulmonary dysplasia. Maintaining an arterial oxygen tension above 85 torr is desirable. Occult, sometimes life-threatening hypoxemia has recently been described in patients with bronchopulmonary dysplasia who have relatively mild clinical disease. Such infants benefit from a predischarge evaluation of gas exchange in all activity states by continuous transcutaneous monitoring of blood gas measurements so that supplemental oxygen can be prescribed for vulnerable periods during daily activities.

Lung reinjury must be avoided. Intercurrent infections—including extrapulmonary infections—should be treated aggressively, and influenza prophylaxis and treatment should be undertaken for any infants older than 6 months. Pertussis immunization is essential even for those infants receiving anticonvulsant therapy. Gastroesophageal reflux must be treated aggressively to avoid aspiration reinjury. Environmental sources of lung injury such as pollution, side-stream cigarette smoke, and exposure to talc should be avoided.

The recovery from bronchopulmonary dysplasia is associated with normal growth and repair of the respiratory tract. Growth failure frequently occurs as a consequence of chronic hypoxemia, increased oxygen consumption, and an inadequate intake of protein and other calories compared with the increased caloric expenditure. Therefore, continuing nutritional assessment and management are important.

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Transient Erythroblastopenia of Childhood

TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD (TEC) is characterized by the gradual development of anemia—a hemoglobin level of 2 to 8 grams per dl—reticulocytopenia, and a pronounced reduction of bone marrow erythroblasts. The platelet count is normal to increased. The leukocyte count is usually normal, although 20% of children may have significant neutropenia (less than 1,000 neutrophils per μl). The disorder occurs in previously healthy young children from 6 months to 4 years of age and is seen with equal frequency in boys and girls. Occasionally cases of the disorder occur in clusters, suggesting it may be a consequence of some seasonal environmental toxin or virus. To date, however, serologic studies have failed to reveal exposure to a common virus. Published data suggest that anemia is due to a transient antibody-mediated suppression of normal erythropoiesis.

The natural history of TEC is that all patients recover spontaneously in a few weeks and there are no long-term hematologic sequelae. In many children with the disorder, particularly if there is evidence of recovery at the time of diagnosis, no specific therapy other than careful observation is necessary. Erythrocyte transfusions are indicated only if a child is symptomatic from the anemia. Neither iron nor steroid therapy has any role in the management of this disorder.

The diagnosis often is confused with that of iron deficiency anemia, although the erythrocytes in patients with TEC are normocytic (mean corpuscular volume [MCV], 70 to 85 fl), whereas iron deficiency anemia is characterized by microcytosis (MCV, 50 to 70 fl). Transient erythroblastopenia of childhood also may be confused with Blackfan-Diamond anemia, although the latter generally presents before 6 months of age, often is associated with congenital abnormalities, and invariably is characterized by macrocytic erythrocytes (MCV, 85 to 100 fl) with many fetal-like features. Because some children with TEC also have significant neu-

tropenia, there occasionally is confusion with the diagnosis of aplastic anemia or acute leukemia, but this is readily clarified by examining the bone marrow.

Reports recognizing TEC as a distinct disorder first appeared in 1970. The general impression among most pediatric hematologists, however, is that the incidence of this acquired erythrocytic aplasia in children is increasing. At our own institution, three cases of TEC were diagnosed from 1979 to 1982, whereas 29 children with TEC were seen from 1983 to 1987. Because the magnitude of anemia in this disorder is usually severe, it is unlikely that it previously existed as an unrecognized condition that is now being more readily recognized.

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Adolescent Suicide and Depression

SUICIDE IS THE THIRD LEADING cause of death in adolescents (aged 10 to 19 years), with a 1985 rate of about 9 deaths per 100,000 in this population. Of all deaths during adolescence, 14% are a result of suicide. Rates differ greatly by age, race, and gender; white and Native American male adolescents in the 15- to 19-year-old group have the highest rates. Since 1960, the incidence of suicide has increased by 200% in the 15- to 19-year-old age group. The frequency of nonfatal attempts and gestures is difficult to document. It is estimated that for every completed suicide, there are 50 to 200 attempted suicides, with a female preponderance in this group as compared with a male preponderance in completed suicides. Cluster suicide, the occurrence of multiple suicides in a circumscribed geographic location during a short time period, has recently appeared. The media have been implicated as an etiologic agent in these suicides because of imitative behavior in the suicidal acts following newspaper stories and televised movies.

Methods used include firearms for boys and girls, with hanging and jumping as the second method for boys and girls, respectively. Drug overdosing is the most common method of attempted suicide but remains uncommon in completed suicides.

Common etiologic factors include a family history of completed or attempted suicide, a previous suicide attempt, substance abuse, aggressive or impulsive behavior, depression associated with behavior problems in male adolescents, sexual abuse, depression, manic-depressive psychosis, learning disorders, and knowing someone who committed or attempted suicide. Certain precipitating events that occur before the suicide attempt include conflict with a parent or friend that is experienced as rejection, anxiety over change, substance abuse, school problems, social isolation, hypochondriasis, pregnancy, and trouble with the law.

Depression remains the common etiologic feature in adolescent suicide, with reported incidence rates of 1.0% in boys and 1.5% in girls; yet the diagnosis in an adolescent remains difficult because the signs and symptoms are more often depressive equivalents and often are attributed to normal adolescence. Depressive equivalents include a decrement in school performance, problems with the law, hypochondriasis, substance abuse, and family conflicts. Adolescent depression has three common features: changes in mood and relationships, thinking, and bodily functioning. Genetic predisposition is increasingly a cause of depression, especially in those young people whose depression begins in childhood and adolescence.

Adolescents who are depressed or contemplating suicide are difficult to engage in treatment. Special attention should be given to those with a family history of suicide, street youth, pregnant girls, and teenagers who have problems with the law. Intervention should focus on querying all adolescents about their feelings of sadness and suicidal ideation, informing young people about mental health problems and the availability of resources, de-emphasizing the romanticization of suicide as portrayed in the media, and engaging depressed and high-risk adolescents in appropriate therapeutic environments.

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Editorials

Local Planning for Health Care

ELSEWHERE IN THIS ISSUE Kizer and colleagues address the relationship of higher levels of government, particularly state government, to local participation and community planning, with respect to the prevention and treatment of the acquired immunodeficiency syndrome (AIDS). The article succinctly reviews the many facts and ramifications of this fatal disease that is spreading so inexorably in California and elsewhere and calls attention to the great diversity of the state. In a sense, California seems so large and diverse that some think of it as more than just a state within a nation, though that is all it is. To be sure its resources and life-styles abound, but too often they are stressed in many ways. The AIDS epidemic is an example. Some counties report no cases, while others have such large numbers that the health care systems in those counties have begun to be seriously strained. There are identifiable population groups at greater risk, but there also seems to be a gradual appearance of the disease in regions and groups hitherto thought to be free of it. Much of this is true in other states as well.

Recognizing the reality of this diversity, Dr Kizer and colleagues in the California Department of Health rightly decided that something other than a purely bureaucratic or centralized state plan was needed. Some supervision and coordination by the state agency would obviously be necessary if there were to be a coordinated approach to the problem and if there were to be some reasonable accountability for public funds appropriated by government for AIDS. But to make it work where the human and health care problems really are, there must also be substantial emphasis on community involvement and local planning to develop the all-important local community commitment and community resources that will be needed to meet unprecedented or soon to be unprecedented local needs. He has, therefore, proposed a model for local planning for AIDS prevention and treatment to be integrated with state coordination and some overall state supervision. It remains to be seen how well this model will work, but it certainly makes sense and deserves a try.

Why does it need a try? When one thinks about it, experience has begun to show that government programs that ignore the realities of local diversity and individual and local community needs and fail to take local perceptions and community resources into account have generally not worked very well. They have often wasted opportunities, not to mention dollars, and too often have created many more problems than they have solved. This has been especially true when the issues are complex and there are no simple answers.

Although not addressed in the article as written, one can sense some potentially far-reaching implications of the AIDS epidemic on the health care system and even on the way we do things in this nation. There are the as yet to be fully understood issues of ever increasing complexity and interdependence in health care itself, and in society as a whole, which in health care at least, are even now reflected in unacceptable and as yet uncontrollable costs. And then there are the even larger problems of the inevitably increasing health care expectations and needs to be matched with what will be, for at least the foreseeable future, always relatively limited resources available to meet either the expectations or even the obvious needs for health care. One wonders whether the AIDS epidemic will somehow serve to bring all this into focus, and so become a force for a more caring, more comprehensive, realistic, and yet more cost-sensitive and cost-effective approach to health care in this nation. If this were ever to happen, and even if it does not, it seems obvious that in the years ahead there will have to be more local and community participation and resources in the planning and delivery of health care.

Dr Kizer's model for state government partnership in local planning for AIDS prevention and treatment could prove to be an important step in the right direction.

MSMW

New Facts About Fat

OUR UNDERSTANDING of the pathogenesis of obesity is finally beginning to emerge from mythology into the realm of biologic science. The widely held, simplistic notion that all of our obese patients are gluttons is passing without too much regret. The latest scientific evidence regarding potential defects that lead to altered energy balance and accumulation of body fat is well summarized in this issue of the journal, in the first of two papers by Bray and Gray.

Two important issues deserve emphasis. First, it has become clear that the resting metabolic rate, representing 70% of total energy expenditure, is an important determinant of body fatness and further, from the studies of Bogardus and colleagues[1] that the metabolic rate may be genetically determined. Thus, a subset of obese persons may exist with low resting metabolic rates, which could in part explain the consistent observation in population studies—in which most people would be in energy balance, that is, at stable weight—that fatter people eat less than do thinner ones. An exciting finding is the suggestive evidence that weight gain is more likely to occur in those with a lower metabolic rate in relation to lean body mass. This observation was made in a population with a high genetic predisposition to obesity and may not be applicable to adult weight gain, where long-term minor degrees of caloric imbalance are unlikely to be detectable by current measures of energy expenditure. Nevertheless, it surely will focus research activities on inherited mechanisms at the cellular and genetic level that might lead to relatively impaired energy expenditure, thereby influencing total adipose mass. A large gap in our knowledge (and in the review article as well) appears to be in our understanding of the pathways and signals for coupling long-term changes in energy expenditure to food intake and fat storage or mobilization in stable obese and thin persons. Bray and Gray rightly conclude that as yet we have no convincing evidence for any principal pathogenetic mechanism in obesity, but I think we are now in a position to ask pointed and meaningful questions.

The evidence that obesity is not only familial—a mix of common environmental and genetic factors—but is also inherited is accumulating and is also beginning to clearly indicate that different forms of obesity exist in humans. This pinpoints the critical necessity for pathophysiologic differentiation among what are likely to emerge as several distinct forms of obesity, with different pathogenesis and diverse health consequences.

This leads to the second issue—the regional distribution of adipose tissue. From the pioneering studies of Vague[2] to the more recent studies in the laboratories of Björntorp[3] and Kissebah,[4] it has become clear that the mechanisms and the metabolic and medical consequences of abdominal adiposity ("android," or upper body) are vastly different from those of adiposity distributed mainly around the hips and thighs ("gynoid," or lower body). Abdominal obesity tends to have its onset in adulthood and is associated with potentially reversible adipocyte hypertrophy, while lower body obesity tends to be lifelong and associated with less readily reversible adipose cell hyperplasia. While large population studies uniformly show increased mortality at body weights about 30% above arbitrary standards, newer data suggest that many of the major causes of death—premature coronary heart disease, diabetes, hypertension—are predominantly associated with abdominal obesity. Fortunately, in the measurement of the waist-to-hip ratio, we have a simple, inexpensive, noninvasive test requiring a minimum of equipment (a tape measure) and minimal need for standardization. Focus must now be on the metabolism of abdominal (particularly abdominal visceral)[5] fat cells in these persons and, at the least, mechanisms for insulin resistance.

The newer insights have important implications for treatment, since we seem to be on the verge of new approaches and new methods of therapy. Bray and Gray, in the second of their two articles, to be published in the November issue of the journal, emphasize, however, that current treatment modes are palliative, not curative, and that recidivism is the rule. This may reflect problems inherent in the current approaches that consider obesity as a single entity for purposes of treatment. Perhaps we would be more successful if we intensively managed those patients at highest risk for the consequences of obesity, such as those with abdominal obesity, and defer attempting nutritional and behavioral approaches for those with lifelong and lower body obesity. This might not be acceptable cosmetically, but it may increase our therapeutic success and, more important, reduce the morbid consequences summarized in the two articles.

Those subsets of obese persons that would appear to benefit most from successful therapeutic attempts at weight reduction include all with an abdominal distribution of adiposity (high waist-to-hip ratio), those with hypertension, type II diabetes, and with certain forms of genetic hyperlipidemia, particularly familial-combined hyperlipidemia.[6]

Modes of therapy for obesity have not really changed in the last decade, except for refinement of nutritional, behavioral, and operative approaches. Drug therapy is still based largely on catecholamine neurotransmitters to suppress appetite and has had little long-term success in maintaining reduced weight. It is associated with a plethora of side effects and a varying propensity for abuse. Drug-enhanced thermogenesis, thyroid in pharmacologic doses, for example, is not useful, since a decline in lean body mass usually exceeds that of fat mass. Fooling the gut by ingesting nonabsorbable materials, such as fiber or sucrose polyester, is likely to result in an increase in intake of absorbable nutrients over the long term to maintain body adipose mass.

We eagerly await the development of new tools that focus on alteration of the endogenous determinants of energy expenditure and its coupling to energy intake. When applied to appropriate subsets of the obese population, newer approaches can be expected to improve the long-term goal of maintaining reduced adiposity.

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A Fantasy of the Future

AT THIS WRITING there seems to be little doubt that a fundamental change is taking place in the Soviet Union, change that was unthinkable only a short time ago. How deep the change is, or how long it will last, we do not yet know, but what we have seen so far could be described as the beginning of an "Americanization" of the Soviet Union, with more permitted in the way of openness, free expression, contested elections, and even some free enterprise. One can sense the beginning of a military retrenchment around the world. If all of this and more is for real, then it could be viewed as a major victory for the free world in what has been an ideologic struggle that threatened the destruction of humankind.

If one recalls some history that is within the memory of many of us, this will not be the first time that "Americanization" has come about in nations that sought to impose their way of life on the rest of the world. After Germany and Japan were vanquished in World War II, both West Germany and Japan subsequently adopted many American ways of doing things. Since the Korean War much the same thing has happened in South Korea. And most significantly, each of these nations, through determination and hard work, has become a formidable economic competitor of America. Some think they may even be outdoing us at our own game!

Now the Soviet Union seems to be trying its hand at some of the American ways of doing things. It is conceivable that much the same thing may happen in China, Central and South America, and perhaps eventually even in India.

One can wonder if we are not somehow shackling ourselves unduly with too many laws and too much paralyzing litigation that sap our vigor, in a sense trying to compete with the rest of the world with one hand tied behind our back. Health care is a case in point. There is growing evidence that too many laws, too much litigation, and too much regulatory interference have already begun to sap the vigor and effectiveness of health care in this nation. The national priorities, whether in health care or in the preparation of our youth to meet the challenges of the future that is before us, seem to fall considerably short of what one would hope and expect if this nation expects to compete effectively in an "Americanized" world that we will have done so much to create. MSMW

Case Reports

Taste Disorder From Zinc Deficiency After Tonsillectomy

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A NUMBER OF DRUGS, diseases, and deficiency states can disturb the sense of taste, and when the cause is correctly identified and treated, the taste dysfunction may be completely reversed. We report the cases of two patients whose taste disorder after a tonsillectomy subsided when zinc deficiency was identified and corrected, and we review the literature regarding zinc deficiency and taste dysfunction.

Reports of Cases

Case 1

The patient, a 27-year-old woman, was seen in November 1986 with a sore throat. Her pharynx was inflamed, and the tonsils were enlarged with numerous exudate-filled crypts. She reported six previous episodes of tonsillitis that year but was otherwise well. Her only medications were iron and calcium supplements. A complete blood count was normal.

In January 1987 she underwent an elective tonsillectomy under general anesthesia, receiving fentanyl citrate, midazolam hydrochloride, pentobarbital sodium, isoflurane, tubocurarine chloride, and succinylcholine chloride. The peritonsillar area was infiltrated with bupivacaine hydrochloride and epinephrine. In the postoperative period she received cephapirin sodium, droperidol, acetaminophen with codeine, and penicillin V potassium. Three days later she took prochlorperazine maleate suppositories for migraine with nausea, and dystonia of the face, jaw, and neck developed that responded to the intravenous administration of diphenhydramine hydrochloride. She had no complaints at a follow-up evaluation four days later, but 5½ weeks after her tonsillectomy she reported a disturbance of taste that had been present since her operation. No abnormality was noted on an ear, nose, and throat examination, and sinus films were normal.

On further questioning she said she noted a disagreeable metallic taste "like a mouth full of pennies" when she awoke from anesthesia. She assumed it would go away, but it had persisted for two months. It was always present but aggravated by consuming fruits, juices, or carbonated drinks, which she had given up. She continued to eat breads, cereals, vegetables, meats, fish, fowl, milk and dairy products, and coffee and condiments, but she complained that most were tasteless, "like Crisco," or that they tasted metallic or bitter. She could faintly taste salt if she added a lot of it. She said her sense of smell was not impaired. Her weight had remained stable. Her only complaint on the systems review was slight cold intolerance.

Findings from liver and thyroid function tests and hepatitis studies were normal, but her serum zinc level was low at 50 μg per dl (normal, 70 to 150).

She was given zinc sulfate, 220 mg twice a day. In one week her serum zinc level had risen to 78 μg per dl, at two weeks it was 72 μg per dl, and at three weeks it was 99 μg per dl. She began to regain normal taste function after ten days, with sweet being the first to return, then salt and bitter, and finally sour on the 20th day of treatment. The metallic taste disappeared after 22 days. She took zinc for another two months; two weeks after stopping therapy her serum zinc, iron, and copper values were normal at 83, 125, and 156 μg per dl, respectively. A month after stopping oral zinc supplementation, her serum zinc level remained normal at 98 μg per dl and her 24-hour urinary zinc excretion was normal at 261 μg per 24 hours.

Case 2

The patient, a 34-year-old woman, was seen in mid-February 1987 with a history of recurrent tonsillitis and strep throat at about monthly intervals for a year. Her weight had dropped from 49 to 45 kg (108 to 99 lb). She had a prolonged episode of influenza in December 1986, but said she had no other illnesses and took no medications. She did not smoke or drink and said her diet had been well balanced. On March 6, 1987, she underwent an elective tonsillectomy with general anesthesia using fentanyl, pentobarbital sodium, isoflurane, atracurium besylate, succinylcholine, neostigmine methylsulfate, and glycopyrrolate.

Postoperative medications included droperidol, morphine sulfate, penicillin V potassium, and acetaminophen with codeine.

She ate sherbet and ice cream in the first week after the operation but they tasted bitter and sour, though gelatin dessert and broth were not unpleasant. When she resumed her usual diet, she noticed that most foods had no taste. She could taste potato chips, and she salted her other foods heavily. All sweet foods tasted bitter, and she avoided them. She did consume breads and cereals, fruits and juices, vegetables, meats, fish and chicken, cheese, soda pop, and condiments. She avoided milk and ice cream, and she had never used coffee. She said foods often tasted spoiled or scorched. She estimated her food intake was less than half what it used to be. Her weight had been as low as 40 kg (89 lb), and she weighed 42 kg (93 lb) when seen in the clinic on August 5, 1987.

In addition to her dysgeusia, she said she had noted difficulty swallowing and articulating after her tonsillectomy, and fluids had regurgitated through her nose. She said she did not have diplopia, ptosis, or limb weakness. A cineesophagogram on April 8, 1987, was normal, and by August 1987 these symptoms had resolved.

The results of a neurologic examination were normal except for the sense of taste. She was unable to taste weak or intermediate sucrose solutions but said a 40% solution tasted "faintly sweet." A weak citric acid solution tasted normal, "like lemon." She perceived a weak salt solution as "awful" and later identified it as salty. A weak quinine solution was

(Bicknell JM, Wiggins RV: Taste disorder from zinc deficiency after tonsillectomy. West J Med 1988 Oct; 149:457-460)

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described as "horrible, hot, awful, and nauseating," and she rushed retching to the sink to rinse her mouth.

A serum zinc level was normal at 99 μg per dl, and an alkaline phosphatase value was normal at 61 IU per liter, but a 24-hour urine zinc excretion was low at 133 μg per 24 hours (normal, 150 to 1,250 μg per 24 hours).

She was given zinc sulfate, 220 mg twice a day. Her taste returned in the second week of treatment and by 14 days was entirely normal. She resumed eating all of her usual foods with full, normal, enjoyable taste and gained 0.7 kg (1½ lb) in the next three weeks. Taste testing after a month of therapy showed normal perception of the weakest solutions of sucrose, citric acid, salt, and quinine, with none of the disagreeable responses seen earlier. Her serum zinc value 17 days after stopping therapy was normal at 111 μg per dl.

Discussion

It is estimated that about 2 million people in the United States suffer from disorders of taste or smell, or both, and, in addition to the psychological impact and altered quality of life, they are at risk for malnutrition, susceptible to gas or food poisoning, and handicapped in such endeavors as professional or domestic cooking.[1] Taste is mediated by taste buds with clusters of 50 or so cells constantly being renewed on a ten-day life cycle, which can be interrupted by disease, nutritional deficiency, radiation therapy, chemotherapy, hormonal alterations, drugs, or aging. Cranial nerves VII, IX, and X carry impulses from the taste buds to the nucleus solitarius in the brain stem, from which they are relayed to the thalamus and cortex. The senses of taste and smell, plus the sensations from free nerve endings of the oral and nasal cavity that respond to temperature, texture, and spices all interact in the perception of flavor, which is immeasurably more complex than the elemental tastes of sweet, sour, salt, and bitter distinguishable by the taste buds alone.[1] Taste and smell disorders may at times result from local chemical injury to the mucosa, from the perception of disease-induced abnormal substances in mucosal or salivary secretions, or from the chewing of medications that damage receptors. The commonest causes of impaired taste, however, appear to be drugs, diseases, or other processes that disrupt the renewal cycle of taste bud receptor cells.[1]

Disturbances of taste include ageusia (absent taste), hypogeusia (impaired taste), and dysgeusia (distorted taste). The severity of taste disorders has been graded I to IV according to the number of items perceived as abnormal from six basic food groups—cereals, fruits, vegetables, meats, dairy products, and miscellaneous (beverages and condiments)—involved.[2] Type I is disturbed taste for only a single food item. Type II involves several but not all items in any group. In type III, all items in one to five groups are involved, and type IV is global, including all items in all food groups. The severity of the taste disorder seemed not to correlate with the cause of the dysfunction, at least in this report. On the other hand, the consequences of taste disorders are strikingly related to the severity. Weight change is negligible in types I and II but averages 5% in type III and 11% in type IV dysgeusia. Further study[3] shows normal caloric intake (2,000 kcal per day) in types I and II, with only vitamin C deficiency; in types III and IV, caloric intake is reduced to 1,500 kcal per day, with a weight loss of 0.6 kg (1.3 lb) per week and several indices of malnutrition including deficiencies of vitamins A and C and of zinc and calcium and in cancer patients a deficiency of meat protein. When the sense of taste and smell is merely reduced but not distorted—hypogeusia and hyposmia without dysgeusia—caloric intake is not impaired.

In addition to nutritional problems, patients with dysgeusia may show mood changes and food avoidance habits that can easily be mistaken for psychiatric illness with olfactory or gustatory hallucinations or for conditioned taste aversions like those seen in patients on cancer chemotherapy.[4] A further constellation of symptoms may be seen with dysgeusia as a reflection of the underlying etiologic dysfunction. For example, Henkin and co-workers described the cases of patients with dysgeusia during histidine treatment of systemic sclerosis in whom anorexia, dysosmia, mental changes—including depression, paranoia, aphasia, agnosia, amnesia, and lethargy—cerebellar dysfunction (tremor, ataxia, and dysarthria), and oral ulcers also developed.[5] The patients were found to have increased urinary zinc excretion and decreased serum zinc levels, and treatment with oral zinc, even with continued histidine administration, reversed all of these symptoms within one to four days.

The etiology of special sense disorders varies with the constellation of senses affected. An isolated loss of smell usually results from viral infections, aging, head injury, or local nasal obstruction; a simultaneous disturbance of smell and taste is seen in association with influenza or hepatitis. An isolated loss of taste, however, is generally referable to drug therapy or deficiency diseases.[1] Common offending drugs include penicillamine and captopril (both with active sulfhydryl groups that may bind zinc), nifedipine (a blocker of calcium channels that are important in taste bud function), plus a long list of anti-infective, antirheumatic, antiproliferative, anesthetic, and other agents[1,4-6] that apparently impair the repair cycle of taste bud receptor cells either directly or indirectly (Table 1). In addition, a number of systemic disorders including neurologic, nutritional, endocrine, local, infectious, gastrointestinal, renal, neoplastic, and other diseases[1,6,7] can cause a disordered taste (Table 2).

The relationship of zinc deficiency to taste disorders may be more pervasive than it would at first appear. Zinc-deficient patients often have a constellation of symptoms, including anorexia, impaired taste and smell, mental impairment, psychiatric disorders, cerebellar ataxia, skin disorders in a perioral and perianal distribution, diarrhea, immune deficiency, impaired wound healing, impaired sexual function, impaired vision, and growth retardation (Table 3).[8-10] Many of these symptoms have been recognized as common accompaniments of dysgeusia. Furthermore, a number of the disorders known to cause dysgeusia are also recognized causes of zinc deficiency, including alcoholism, malnutrition, cirrhosis, malabsorption, renal failure, surgical stress, burns, and a number of drugs such as penicillamine and histidine.[7-11] In addition, the dysgeusia and other symptoms in these patients often are responsive to zinc replacement.[7-10] Henkin and associates found low serum zinc levels in patients with idiopathic hypogeusia,[12] and treatment of hypogeusic patients with zinc replacement corrected many related symptoms and improved taste thresholds in a single-blind treatment trial.

The mechanisms by which zinc deficiency impairs taste are unclear. It is known that zinc is an important cofactor for alkaline phosphatase, the most abundant enzyme in taste bud membranes; it is also a component of a parotid salivary protein important to the development and maintenance of

normal taste buds.[5] Catalanotto and Nanda proposed five possible mechanisms for taste dysfunction in experimental animals[13]: impaired protein synthesis in taste bud cells, reduced alkaline phosphatase activity in taste buds, an abnormality of the zinc-containing salivary protein, a blockage of pores in taste buds, or some form of central nervous system dysfunction.

The origin of the zinc deficiency in our patients remains unclear. The iron supplement in case 1 may have been a factor because iron and zinc compete in the absorptive pathway.[14] The frequent episodes of tonsillitis in both patients in the year preceding surgical treatment raise the possibility of chronic zinc deficiency with impaired immune function, but we have no information regarding the preoperative zinc levels or tissue stores. The stress of an operation may have further lowered zinc levels. Surgical procedures of the head and neck are known to cause dysgeusia,[5] and zinc deficiency has been described in surgically treated patients,[15] but zinc-deficient dysgeusia has not previously been described after tonsillectomy. Though the mechanism of surgery-related zinc deficiency is not stated, it is known that interleukin 1 levels rise in response to stress of many sorts and that it promotes the redistribution of zinc from the serum to tissues such as the liver.[8] Medications may also have contributed to the dysgeusia in these patients. Fentanyl, morphine, and codeine (opioids); bupivacaine (a local anesthetic); cephapirin sodium and penicillin V potassium (antimicrobials); droperidol and prochlorperazine (neuroleptics); and diphenhydramine hydrochloride (an antihistamine) are all at least similar to drugs known to disturb taste or smell.[1] Holding the mouth open for tonsillectomy could possibly stretch the nerves for taste, but dysgeusia has not previously been reported in patients having tonsillectomy or oral operations; furthermore, in that case a gradual recovery after the operation would be expected. In our patients, however, the taste dysfunction persisted unaltered for three months in case 1 and four months in case 2 and then was recovered fully in three and two weeks, respectively, with correction of the zinc deficiency.

TABLE 1.—*Drugs Causing Zinc Deficiency, Taste Dysfunction, or Both*

Pharmacologic Activity	*Drugs*
Chelators	o-Penicillamine, histidine
Anti-infective	Griseofulvin, metronidazole, rifampin, tetracycline
Psychoactive	Amphetamines, imipramine hydrochloride, lithium carbonate, trifluoperazine hydrochloride
Anticonvulsants	Carbamazepine, phenytoin
Miscellaneous	Acetazolamide, captopril, clofibrate, iron, nifedipine

TABLE 2.—*Diseases Causing Zinc Deficiency, Taste Dysfunction, or Both*

Disease Category	*Disease*
Infection	Hepatitis, viral upper respiratory tract infection
Gastrointestinal	Enteritis, colitis, malabsorption
Nutritional	Alcoholism, cirrhosis, intravenous fluids, total parenteral nutrition
Rheumatic	Sjögren's syndrome
Renal	Uremia, dialysis
Neoplasm	Cachexia, chemotherapy
Stress	Burns, trauma, surgical treatment
Endocrine	Pregnancy, contraceptives, hypothyroid
Neurologic	Head injury, cranial nerve injury
Hereditary	Acrodermatitis enteropathica
Local	Smoking, radiation, rhinitis, dental
Idiopathic	

TABLE 3.—*Clinical Manifestations of Zinc Deficiency*

Disorder	*Clinical Manifestation*
Skin lesions	Crusting facial and perianal rash
Vision impairment	Impaired retinal dark adaptation
Hypogonadism	Reduced potency, libido, fertility
Anorexia	Impaired taste, smell, appetite
Impaired wound healing	Reduced DNA, RNA, and protein synthesis
Congenital malformation	Miscarriage, malformation, ? fetal alcohol syndrome
Immunodeficiency	Impaired cellular immunity, increased infection
Carcinogenesis	Impaired immune surveillance; head, neck, and esophageal neoplasms
Mental changes	Apathy, irritability, confusion, depression
Diarrhea	Causes further zinc loss
Growth retardation	In children
Cerebellar dysfunction	Tremor, ataxia, dysarthria

The laboratory diagnosis of zinc deficiency is most easily made by showing a low serum zinc level in a patient with appropriate symptoms or in a high-risk clinical setting.[16] A reduced urinary zinc excretion suggests depleted body zinc stores.[9] Levels of alkaline phosphatase, carboxypeptidase, or thymidine kinase, enzymes that are highly zinc dependent, may be depressed when a serum zinc level is low.[9] Studies of hair, erythrocyte, or leukocyte zinc levels are also used at times, but these assays are technically more difficult and not necessarily more reliable than serum and urine zinc tests (C. J. McClain, MD, oral communication, Mar 1987). The plasma copper:zinc ratio has been studied, but the origin and significance of altered ratios remain uncertain.[9]

The treatment of dysgeusia consists basically of correcting specifically identified underlying disorders. In the case of zinc deficiency, oral supplementation with zinc sulfate, 440 mg a day in divided doses[5] or 15 to 25 mg of zinc per day in the form of zinc acetate or gluconate,[9] has been effective. When effective, zinc therapy probably truly reverses a zinc deficiency or binds the active sulfhydryl group of an offending drug. In the absence of a proven zinc deficiency, double-blind studies of zinc therapy show no benefit. Nonetheless, many patients recover spontaneously as zinc-depleting drug therapy is stopped or precipitating illnesses subside and the natural cycle of taste bud repair is restored.[1] Long-standing cases, however, seem remarkably resistant to treatment, and change, if any, is likely to be in the direction of a gradual worsening.[2] Even so, such patients may benefit from nonspecific measures such as chewing gum or ice chips or using mouth washes of sodium bicarbonate, artificial sweeteners, or local anesthetics.[1]

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Penicillin-Induced Agranulocytosis

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SYSTEMIC PENICILLIN THERAPY is generally the treatment of choice in patients with bacterial endocarditis. Prolonged therapy at a high dosage is often required. Complications of treatment with penicillin, although uncommon, include hypersensitivity reactions ranging from mild urticaria to life-threatening anaphylaxis, central nervous system disorders, electrolyte disturbances, and acute interstitial nephritis. Hematologic complications of hypersensitivity to penicillin are rare. Coombs' test-positive hemolytic anemia has been reported.[1,2] Leukopenia also occurs, with 26 cases being reported to date. Agranulocytosis, however, has been previously reported only once, in 1946.[3] Herein we report a second case of agranulocytosis as a complication of penicillin therapy.

Report of a Case

The patient, a 17-year-old woman, presented with a three-week history of nocturnal fever not associated with rigors or chills. She had had generalized myalgia for two weeks and a generalized maculopapular rash for one week. Her family physician recorded a mitral regurgitant murmur and referred her to our hospital. There was no history of rheumatic fever, and her last dental visit was three months before the symptoms began.

On physical examination on admission she had a grade III/VI pansystolic murmur at the apex and a maculopapular rash over her extremities, but the results were otherwise normal. A chest x-ray film and an electrocardiogram were normal. Two-dimensional echocardiograms showed mitral valve prolapse with no valvular vegetations.

A clinical diagnosis of infective endocarditis was made and confirmed by identifying viridans group streptococci in each of nine blood cultures. The organism was sensitive to penicillin in vitro. Laboratory findings included the following: hemoglobin, 134 grams per liter; leukocyte count, 16.9×10^9 per liter, with 62% neutrophils and 24% lymphocytes. The urea, creatinine, electrolytes, plasma proteins, and liver enzyme levels were normal.

The intravenous administration of penicillin G sodium, 3 million units every six hours, and streptomycin sulfate, 100 mg given intramuscularly daily, was begun. Five days after starting treatment the patient was asymptomatic. On day 17 of her hospital stay, the streptomycin therapy was discontinued. The patient continued to do well until day 23, when she complained of a sore throat. Her leukocyte count was 3.2×10^9 per liter. Neutrophils were absent; the nucleated cells were predominantly atypical lymphocytes. Her hemoglobin was 130 grams per liter and the platelet count 332×10^9 per liter. A Coombs' test and assays for hepatitis B-associated antigen, heterophile antibody, antinuclear antibody, and rheumatoid factor were all negative. Serum immunoelectrophoresis showed an increase in polyclonal immunoglobulin (Ig) M and IgG. C3, C4, and CH_{50} assays were all negative.

A bone marrow aspirate showed normal cellularity with normal erythropoiesis. The myeloid:erythroid ratio was 3:1. Granulopoiesis showed no maturation beyond the promyelocyte stage.

Treatment with penicillin was discontinued on day 25, and a regimen of vancomycin hydrochloride was started. Two days later a peripheral blood monocytosis arose, accompanied by the appearance of bands. By day 30 the leukocyte count had risen to 17×10^9 per liter, with 0.48 neutrophils, 0.15 bands, 0.29 lymphocytes, and 0.08 monocytes. On discharge from hospital on day 34, there was no clinical evidence of the original infection.

Discussion

Leukopenia due to penicillin therapy is a rare event; only 26 cases—including this one—have been reported to date. We believe this to be the second report of penicillin-induced agranulocytosis in the past 50 years. In each case of penicillin-associated leukopenia, the patients received high-dosage penicillin for serious systemic infections. In 18 of 26 cases, therapy was for endocarditis. Table 1 summarizes the cases reported to date. All patients received their drugs by the intravenous or intramuscular routes. The earliest that leukopenia was noted was after four days of therapy, although it was seen as late as 35 days after penicillin treatment in one patient. The average duration of therapy before leukopenia occurred was 20 days. The range of total leukocyte counts at the nadir of the leukopenia was 0.1 to 3.9×10^9 per liter. Including our case, the absolute granulocyte count ranged from 0 to 1.998×10^9 per liter. The average granulocyte count was 0.372×10^9 per liter. In keeping with other reports, the total dose at the start of leukopenia was greater than 150,000 units per kg body weight per day.[4] All patients had normal leukocyte counts within 2 to 14 days of discontinuing the antibiotic therapy. The average time to recovery was 4.7 days. There were no deaths or permanent sequelae related to the leukopenia. Five patients had Coombs' test-positive hemolytic anemia.[1,2,5-7]

Bone marrow aspiration was done in 16 cases. The results of the aspirations showed no consistent pattern. Hypercellular, normocellular, and hypocellular marrows have been reported, although a hypocellular marrow was found in only one case.[11] In this case of gonococcal endocarditis, there appeared to be no features distinguishing it from cases associated with hypercellular and normocellular marrows.

Our case is consistent with other reports in total penicillin

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dose, duration of treatment, and duration of leukopenia. While it is possible that the leukopenia may have resulted from sepsis alone, it is more likely that the common factor was high doses of parenteral penicillin. The mechanisms of penicillin-induced leukopenia are as yet not fully understood. At least two distinct mechanisms of drug-induced leukopenia are known,[6,17] and both immunologic (type I) and toxic (type II) factors have been implicated. Antineutrophil antibodies have been detected in seven patients,[5,6,15,16] and circulating antipenicillin antibodies have been described as well.[2,6,18] Moreover, in a case described by Rossiter and co-workers, there was a previous history of penicillin-induced leukopenia.[5] Similarly, in the case described by Petz and Fudenberg, the readministration of penicillin resulted in a recurrence of Coombs' test-positive hemolytic anemia with leukopenia.[2] Interestingly, the initial hemolytic anemia with

TABLE 1.—*Summary of 26 Cases of Penicillin-Induced Leukopenia Reported*

Case	Source	Diagnosis	Age, yr	Sex	Penicillin Dose/d, million units	Days to Onset of Leukopenia	Cell Counts at Nadir (× 10^9/liter) WBC	PMN	%	Days to Recovery	Anti-leukocyte Antibody	Coombs' Test	Bone Marrow
1	Spain and Clark, 1946[3]	Bowel obstruction	54	♂	100,000 U × 1d 160,000 U × 3d	4	0.10	0.00	0	1	...	...	Normal at autopsy
2*	Petz and Fudenberg, 1966[2]	Infective endocarditis	45	♂	100 IV	23	1.60	0.18	11	7	...	Pos	Normal cellularity; decreased granulocyte precursors
3	Forshaw, 1968[8]	Infective endocarditis	47	♂	8 IV × 14d 16 IV × 6d 32 IV × 13d	27	0.95	0.02	2	14	...	Neg	Increased cellularity; no mature granulocytes
4†	Rossiter et al, 1968[5]	Infective endocarditis	37	♂	Phenethicillin, 4 grams PO × 14d, then IM	28	0.80	0.03	4	3	Pos	Pos	Normal erythropoiesis; no mature granulocytes
5	White et al, 1968[1]	Infective endocarditis	64	♀	20 IV	18	3.20	...	...	2	...	Pos	Increased erythropoiesis, left-shifted granulopoiesis
6	Joorabchi and Kohout, 1973[7]	Infective endocarditis	12	♂	20 IV	18	2.30	0.16	7	14	...	Pos	Hypercellular, M:E 3:1, shift toward mature cells
7	Colvin et al, 1974[9]	Infective endocarditis	39	♀	20 IV × 7d 12 IV × 14d	23	0.90	0.08	9	5	Neg	Neg	Hypercellular; increased granulopoiesis
8	Homayouni et al, 1979[4]	Cellulitis	60	♂	230,000 U/kg IV	13	3.70	1.99	54	6	...	...	...
9		Gangrenous appendix	81	♂	250,000 U/kg IV	9	3.70	1.81	49	2	...	...	...
10‡	Neftel et al, 1981[6]	Infective endocarditis	54	♀	12 IV × 18d 32 IV × 3d	20	0.80	0.04	2	2	...	...	...
11‡		Infective endocarditis	28	♂	24 IV	19	2.00	0.10	5	4	Pos	Pos	...
12‡		Infective endocarditis	27	♂	16 IV	21	2.20	0.23	10	2	...	...	Hypocellular; maturation arrest, promyelocyte stage
13‡		Infective endocarditis	39	♂	20 IV	26	2.20	...	...	6	...	...	...
14‡		Infective endocarditis	25	♂	20 IV	24	1.80	...	...	3	Pos	...	Hyperactive marrow
15‡		Pneumonia	35	♂	16 IV	26	3.90	...	...	4	Pos	...	Maturation arrest, myelocyte stage
16		Hemangioma	13	♂	12 IV	19	3.40	...	...	10	Pos	...	Maturation arrest, myelocyte stage
17‡		Septic arthritis	64	♀	20 IV	26	2.50	1.00	40	3	...	...	...
18	Postelnick and Gaskins, 1981[10]	Infective endocarditis	21	♀	16 IV × 14d 20 IV × 3d	15	1.80	0.09	5	2	...	...	...
19§	Timmis et al, 1981[11]	Infective endocarditis	18	♀	20 IV	14	2.60	0.21	8	7	...	...	Hypoplastic
20	Yap, 1981[12]	Infective endocarditis	32	♂	16 IV × 7d 8 IV × 18d	25	1.20	0.21	17	3	...	Neg	...
21	Corbett et al, 1982[13]	Infective endocarditis	28	♂	8 × 20d 13 × 1d	22	0.90	0.40	44	3	...	...	Hypercellular; left-shifted granulopoiesis
22		Infective endocarditis	55	♂	12	35	0.70	0.50	72	2	...	...	Maturation arrest of WBC series
23	Miro et al, 1983[14]	Pleural empyema	40	♂	12	24	3.10	0.31	10	4	...	...	...
24	Rouveix et al, 1983[15]	Infective endocarditis	46	♂	250,000 U/kg IV	25	2.40	0.02	1	4	Pos	...	...
25	Snavely et al, 1983[16]	Infective endocarditis	31	♂	6 IV × 15d 15 IV × 14d	29	2.20	0.06	3	5	Pos	Neg	Hypercellular; increased granulocyte series; paucity of mature forms
26	This report, 1988	Infective endocarditis	17	♀	12 IV	22	3.20	0.00	0	8	Neg	Neg	Maturation arrest, promyelocyte stage

IM=intramuscularly, IV=intravenously, M:E=myeloid:erythroid ratio, Neg=negative, PMN=polymorphonuclear leukocytes, PO=orally, Pos=positive, WBC=lymphocytes

*Leukopenia recurred with the readministration of penicillin.
†Patient had a previous episode of penicillin G-induced granulocytopenia.
‡Data extrapolated.
§Granulocytopenia recurred after cefuroxime sodium and gentamicin sulfate were given.

leukopenia developed in this patient despite the prophylactic administration of prednisone. In another case where no antibodies were detected, the readministration of a single dose of penicillin resulted in a striking drop in the neutrophil count within 24 hours.[7] Although Neftel and associates have described circulating antipenicillin IgG antibodies in all their patients given penicillin in cumulative doses greater than 200 million units,[6,18] leukopenia did not develop in all patients so sensitized. The degree of sensitization may be diminished if the drug is given as a freshly prepared bolus rather than by slow infusion.[18,19]

The reports of neutropenia with the readministration of penicillin and the presence of antipenicillin antibodies favor a type I or hypersensitivity-type reaction. If this postulate is correct, this leaves the question of why antineutrophil antibodies have not been detected more frequently. One possibility is that the antibodies are of low concentration and of high affinity. In this situation, the antibodies would be almost all cell-bound, hence the free, detectable amount in the circulation would be low. If penicillin degradation products are required as haptens for the neutrophils, these would not be detected if fresh penicillin were added to the in vitro assay.[14] The occurrence, however, of penicillin-associated neutropenia in the face of prednisone therapy[1] argues against an immune-mediated reaction.

Another possible mechanism is that of a toxic, dose-related suppression of bone marrow precursors. This mechanism would be independent of circulating antipenicillin or antineutrophil antibodies. The almost invariable association with the administration of high doses of the drug and the fact that the neutropenia seldom occurred before 14 days favor this concept. Alternatively, the high dose and delayed onset may be related to the minimum dose needed for sensitization to occur. Joorabchi and Kohout have postulated that the pancytopenia seen in their patient was due to the penicillin-induced blockade of the release of mature cells from the marrow.[7]

The variation of marrow findings in the reported cases is intriguing and could possibly be explained by variations in the time of marrow sampling. Early in a patient's course, the marrow may be hypoplastic or aplastic and devoid of granulocytes and normoblasts. During the earliest phase of marrow recovery, there may be a transient increase in small dense lymphocytes in the marrow, subsequently replaced by the earliest granulocyte precursors.[17] Later, during recovery, the marrow would be extremely hypercellular with intense mitotic activity. Thus, "maturation arrest"—in which differentiation of marrow cells is considered to halt at a specific developmental stage—may be related only to the phase of recovery of the regenerating marrow.

Leukopenia is a rare complication of systemic penicillin therapy. It almost invariably occurs in cases of prolonged high-dose therapy. Monitoring the leukocyte count regularly during therapy may avert the occurrence of absolute granulocytopenia by detecting leukopenia early. Withdrawing penicillin therapy has resulted in a rapid return to normal of the leukocyte count in all cases.

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Midcycle Pneumothorax in a Patient With Catamenial Pneumothoraces

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CATAMENIAL PNEUMOTHORAX is a syndrome of recurrent pneumothoraces developing within 48 to 72 hours of the start of menstrual bleeding. In most cases they are small, unilateral, right-sided pneumothoraces occurring in parous women in their third and fourth decades. The close temporal relationship to menses has led several authors to conclude that evidence of pneumothorax at other times in the cycle precludes the diagnosis.[1-3] We report the case of a patient with catamenial pneumothorax in whom pneumothoraces developed between menses.

Report of a Case

The patient, a 39-year-old nonsmoking woman, presented for evaluation of recurrent pneumothoraces. She had been admitted to hospital twice with shortness of breath, cough, and chest pain. Chest radiographs showed small right-sided pneumothoraces without other abnormalities. During both hospital stays, therapy included only oxygen and analgesics. She recalled that each admission corresponded with the beginning of her menstrual period. In the following year the same symptoms recurred several times, always within 48 hours of the start of menstrual bleeding, but she saw her physician only when she needed analgesics. On each visit, a chest radiograph showed a small right-sided pneumothorax.

A year after her initial diagnosis, she also noticed shortness of breath, cough, and chest pain between menses. On day 14 of a menstrual cycle, she consulted her physician at the

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start of these same symptoms. A chest radiograph showed a small right-sided pneumothorax.

Her obstetric history revealed seven uncomplicated deliveries and one miscarriage. She had a 28-day menstrual cycle associated with regular menses during which she would have abdominal, rectal, and back pain. Her bleeding was heavy for two to four days and lasted ten days. Endometriosis had been clinically diagnosed, and a trial of a contraceptive drug failed to control her pain. The results of a physical examination were normal.

She was placed on a regimen of medroxyprogesterone acetate in an attempt to control the catamenial pneumothoraces and has been without symptoms of recurrent pneumothoraces or endometriosis during the past nine months with this treatment.

Discussion

This patient has a characteristic presentation for catamenial pneumothorax, with multiple episodes of pneumothorax occurring within 48 to 72 hours of the start of menstrual bleeding; occurring in the fourth decade of life; past pregnancies; and small, unilateral, right-sided pneumothoraces. Her complaint of symptoms and the radiographic documentation of a pneumothorax between menses have not been reported in patients with this disorder. The midcycle pneumothorax occurred 3½ months after her last prior episode and so could not have been the residual of a previous pneumothorax.[4] Several definitions currently in the literature would exclude this patient, but her presentation and response to therapy lead us to conclude she did have catamenial pneumothorax.

The pathogenesis of catamenial pneumothorax is explained by four proposed but unproven theories: thoracic endometriosis, diaphragmatic defects, air trapping and pleural tear due to prostaglandin F_2, and a hormonally mediated rupture of pulmonary blebs.

Clinical and pathologic evidence of pelvic endometriosis was found in 22% to 37% of patients with catamenial pneumothorax.[3] Thoracic endometriosis is found in as many as 35% of patients with this disorder who undergo thoracotomy.[3,5] Ectopic endometrial tissue is postulated to enter the thorax by either hematogenous and lymphatic dissemination or direct extension through diaphragmatic defects. It is hypothesized that hematogenous and lymphatic dissemination to the thorax may follow a normal delivery, abortion, cesarean section, trauma, hysterectomy, and curettage. Embolization of decidual endometrium indicating tissue transport has been found on autopsy of women who die giving birth.[6,7] Hematogenous dissemination of endometrial cells with implantation and growth in the thorax has also been shown in animals.[8]

Diaphragmatic defects have been found in 33% of cases of catamenial pneumothorax.[5] These defects may allow endometrial cells to be implanted directly onto the thoracic diaphragmatic surface, parietal pleura, and visceral pleura.

It has also been suggested that intrapulmonary foci of endometrial tissue could swell, causing a check-valve type of airway obstruction leading to local air trapping, pleural tears, and pneumothorax.[1] Pleural or subpleural foci could slough during menstrual bleeding leading to hemothorax, pneumothorax, or hemopneumothorax.[5] Endometrial implants associated with catamenial pneumothorax are commonly found on the diaphragm at the time of thoracotomy or pleuroscopy.[9-14] A breakdown of this tissue during menses could lead to diaphragmatic perforation and pneumothorax. Diaphragmatic defects of any cause may result in catamenial pneumothorax independent of endometriosis by permitting air to enter from the peritoneum into the pleural cavity. Air is thought to enter both the peritoneum and the pleural spaces from the genital tract as menstrual bleeding displaces mucus normally found in the endocervical canal. The entry of air to the peritoneal cavity from the genital tract has been documented in women.[15-19] Peritoneal air may also follow oral-genital sex, though this patient said she did not partake in this activity.

Researchers postulate a role for the induction of catamenial pneumothorax by prostaglandin F_2, an active airway and vascular constrictor found in high concentrations in endometrial debris. It is proposed that it may cause bronchospasm during the menses, leading to alveolar rupture and pneumothorax.[3]

Finally, it has been hypothesized that in women with this disorder subpleural blebs rupture at the start of the menses.[3,5] Reasons for bleb rupture at the beginning of menses have not been described.

The clinical evidence of pelvic endometriosis raises the possibility of thoracic endometriosis as the cause of this patient's catamenial pneumothorax, but the pneumothorax between menses is difficult to explain given the current theories. It seems likely that the source of air would be the lung rather than the genital tract. The midcycle pneumothorax may have resulted from imperfect regeneration of endometrial tissue in a subpleural location with scarring and possible pleural traction. This may have predisposed the tissue to a spontaneous breakdown independent of hormonal mediation.

This case shows that a diagnosis of catamenial pneumothorax should not be excluded when a pneumothorax occurs between menses if the dominant pattern of pneumothoraces associated with menstrual bleeding is present. Her course also raises interesting questions regarding the origin of these pneumothoraces.

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Debunking Barium Appendicitis

To the Editor: The conclusions drawn by the authors of "Barium Appendicitis" in the April 1988 issue[1] require critical evaluation. They state ". . . and we advocate early appendectomy in symptomatic patients with evidence of retained barium within the appendix." Taken literally this statement may lead to unnecessary surgical procedures.

Clearly, any patient with symptoms of acute appendicitis requires an immediate operation regardless of whether the appendix retains barium. With this title, "Barium Appendicitis," however, the authors imply a cause and effect relationship of intraluminal barium with appendicitis.

The significance of prolonged retention of barium in the appendix has been debated since Bowcock's report in 1935.[2] Of his original eight patients followed for as long as two weeks, none developed appendicitis and two had normal appendectomies. Johnson found barium in the appendix for more than 72 hours in 8% of 1,106 patients.[3] Maglinte and co-workers studied 31 patients who retained barium for as long as 30 days and after a follow-up of 1 to 1½ years, none developed appendicitis. A total of 11 had subsequent films, and barium had disappeared in all.[4]

It is estimated that 3.5 million colon examinations and 6.9 million upper gastrointestinal (GI) series are done in the United States annually (industry data, oral communication). Post-examination appendiceal retention of barium is seen in 90% to 95% of patients, especially after barium enemas.[5] In the overwhelming majority of these patients, appendicitis does not develop.

Do the two case reports support the conclusion that intra-appendiceal barium caused appendicitis? Case 1 revealed barium within the appendix, but no pathologic study was provided to show that it caused the appendicitis. In case 2, the right lower quadrant concretion had a lucent center and a barium rim, suggesting that the barium outlined a preexistent nonopaque fecalith as discussed by Maglinte and associates.[4]

The term "barium appendicitis" is a misnomer, suggesting as it does that barium is the cause of the inflammation. Intraluminal barium is inert and has little physiologic effect on the gastrointestinal tract.[6]

Barium retained in the appendix may have diagnostic value in two situations.[7] A preexisting fecalith may coat with barium and then have some significance as an opacified appendicolith.[5] Also, barium may outline the appendiceal lumen and thus show widening or irregularity as a manifestation of progressing appendicitis.[8]

Millions of barium-based gastrointestinal studies are done in the US each year. Similarly, appendicitis represents one of the most prevalent surgical diseases. By chance alone, appendicitis will develop in a few patients in the days or weeks following a gastrointestinal study. The paucity of reported cases (four of the authors' six references appeared before 1970) attests to the unlikelihood of a causal relationship.

In conclusion, we find no support for the concept of barium appendicitis and agree with Maglinte and colleagues that "Barium appendicitis as an entity should be disregarded and etiologic connotation between prolonged appendiceal barium retention and future acute appendicitis should be erased."[4]

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* * *

Drs Dalessandri and Palder Respond

To the Editor: It is true that barium is inert and barium itself does not cause inflammation. It makes sense, however, that a barium appendicolith can cause inflammation when it causes obstruction. It is commonly accepted that an inert gallstone or kidney stone can cause inflammation when it causes obstruction.

It is also true that postexamination appendiceal retention of barium is seen in approximately 90% of patients after barium enemas. In fact, this is a sign of a normal appendix.[1,2] Most older patients, however, have spontaneous emptying of the barium-filled appendix within 72 hours.[1] Although appendicitis is the most common acute operative condition of the abdomen, it prevails primarily in the second and third decades of life. The two cases of acute appendicitis presented occurred in a 66-year-old and a 45-year-old man several months after receiving barium studies. We are, therefore, speaking of an older age group more likely to receive barium studies and less likely to have the development of acute appendicitis. Further case reports in this area will shed greater light on this subject.

We think that any patient with known prolonged retention of barium in the appendix—more than 72 hours—should be informed of that fact, just as we think any patient with asymptomatic gallstones or kidney stones should be informed. At present we advocate an operation only for those barium appendicolith patients with symptoms consistent with acute appendicitis.

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Why Every Woman Over 40 Isn't in a Breast Cancer Detection Program

To THE EDITOR: Why isn't every woman over 40 in a breast cancer detection program? It is interesting to read the conclusion of Dr Robertson that the reason is poor compliance by physicians with screening recommendations.[1] The recommendations of the American Cancer Society and the American College of Radiology have the prestige, but it takes more than that. There are no uniform standards of care, preventive or otherwise, established by organized medicine or the government. Certainly, there are no mandatory requirements—which might not be a bad idea. The medical background, experiences, and practices of a half million physicians are divergent.

The elderly, the poor, the uneducated, and ethnic minorities are segments of the population not well penetrated by our health crusades. These groups are reluctant to seek medical advice when asymptomatic and often even with symptoms.

The middle class is more responsive to health education. Even here, however, asymptomatic persons have limited time, interest, and resources allocated to health. They are under a constant bombardment by medicine, family, and friends regarding diet, calories, salt, fat, sugar, cholesterol, calcium, vitamins, blood tests, cardiograms, pap smears, exercise, stress management, and so forth. The middle class shows a certain exhaustion from an overdose of health information.

Personality is a major key. Some people love to be medically pampered. They love interviews, examinations, tests, operations, whatever is fashionable. Others are uninterested or fearful of discovering an illness. They deny symptoms and reject an aggressive medical approach. They seek out health practitioners who are less forceful and demanding.

We physicians are also under economic pressures. It is difficult to coax an asymptomatic patient to have routine physicals or preventive tests at a time when insurance companies will not cover them or they carry high deductibles. My perspective is one of the general physician-surgeon: a complex of social, psychological, and economic problems. Why isn't every woman over 40 in a breast cancer detection program? I think that all women are, to the extent reality permits. We cannot force a mammogram as we can force a vaccination for a child or a pap smear for a woman on birth control pills. In spite of these difficulties, the use of mammograms and discovery of early cancers are increasing but not faster than the sophistication and prosperity of the general population.

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Economies of Scale

To THE EDITOR: In your editorial, "On Specialized Centers for Patient Care" in the July 1988 issue,[1] you discussed the economies of scale thought to exist in specialized care centers, and you stated that economies of scale result in better quality of specialized care given at the specialized care center. Improved cost of such care, however, was not confirmed because supporting data were not available.

It seems sensible, a priori, that greater experience derived from providing frequent replication of highly complex care would produce a better technical quality in a shorter elapsed time. But lower costs for this care will not result so long as a piecework payment (fee for service) system exists. If cost economies of scale are to be realized, large-volume, complex technical care will have to be provided by salaried technicians, working at hourly payment rates, with incentives to increase productivity.

Because physician payment is not yet made at hourly rates, it appears ridiculous to expect economies of scale to apply to physician services.

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Fluoride in Mineral Water

To THE EDITOR: Commenting on an article by Russell and colleagues in the November 1987 issue,[1] Dr Robert Isman, Chief, Office of Dental Health, Department of Health Services, State of California, stated that " 'Such heavy exposure is associated with a level of at least 10 ppm in the drinking water supply.' These fluoride levels do not exist in the US, and there have been no reported cases of crippling fluorosis in the United States."[2]

Dr Isman may be correct in asserting that there have been no reported cases of crippling fluorosis in the United States, but he is not correct in assuming that all drinking water supplies are under 10 ppm fluoride level.

In a lawsuit in San Francisco, Burton et al v Source Perrier et al (SF Superior Court Cir No. 810212), the Food and Drug Administration, in response to a Freedom of Information Act request about Calistoga bottled mineral water, provided numerous analyses of expensive bottled drinking water with fluoride levels in excess of 10 ppm. Calistoga Sparkling Mineral Water and Orange Flavored Mineral Water frequently exceeded the fluoride levels Dr Isman asserts do not exist in the US.

Further information may be obtained from Alioto & Alioto, 650 California Street, San Francisco, CA 94108.

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* * *

Dr Isman Responds

To THE EDITOR: Dr LaDou is correct in his assertion that Calistoga bottled mineral water at one time contained fluoride levels in excess of 10 ppm. Since January 1, 1988, however, California law has required mineral water to be treated to reduce the concentration of any naturally occurring substance that exceeds the bottled water safety standards established by the Department of Health Services. For fluoride, these standards limit the concentration to between 1.4 and 2.4 ppm, depending on the annual average of maximum daily air temperatures. Mineral water producers who bottle

5,000 gallons or less per week have until January 1, 1989, to comply with these standards.

The point of my statement was that fluoride levels of 10 ppm *in the public drinking water supply* do not exist in the United States. Calistoga mineral water and several other bottled mineral waters come from thermal aquifers that are not sources of public drinking water. The highest fluoride concentration of any of the several sources of public drinking water in the city of Calistoga is 0.23 ppm.

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On the Meaning of Words

To THE EDITOR: The words research, experiment, and investigate are frequently used interchangeably by members of the scientific community; standard dictionaries consider these words synonymous or analogous. No pertinent references concerning the definition or use of these words could be found in either the medical or legal libraries at the University of New Mexico.

That the concern over the interchangeable use of the words research, experiment, and investigate can be at times more than a mere exercise in semantics was brought to the attention of the authors when, during a recent trial, the plaintiff's attorney informed the jury, with emphasis, that the defendant had performed research on the plaintiff. This, despite the fact the plaintiff's attorney was well aware that the defendant had conscientiously engaged in laboratory research by doing an adequate series of experiments on dogs to investigate (determine) the feasibility of a new operation. The defendant had also presented his data to the Human Research Review Committee of the University of New Mexico School of Medicine.

We suggest that the words research, experiment, and investigate be reserved for the chemistry, biology, or animal laboratory and recommend that when the use of a new drug, device, procedure, or operation is applied to humans, the term clinical trial be used. In time, the distinction between laboratory research and clinical trial will, we hope, become more universally accepted. This would ameliorate confusion and the implication of assault on the human body. It might further deny some future plaintiff's attorney the opportunity of inaccurately implying that the defendant has treated a patient improperly.

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The Yin and Yang of Medical Practice

To THE EDITOR: I congratulate Drs Botticelli and Gilbert for attempting to clarify, in the July 1988 issue, the two factions of modern medical practice by presenting these aspects within the context of the yin yang wisdom.[1]

If we are truly sincere in our effort to bring a balance between the personal aspect of medicine—the patient/doctor/illness—and the impersonal aspect—technology, business, and politics of medicine—within the context of yin yang, we must start with the correct premise. For this we need to return to the I Ching, which states the positions of yin (earth) and yang (heaven) and what they further represent.

"Yang—the Creative is heaven, metal, cold, ice, the father . . .

"Yin—the Receptive is the earth, the mother. It is cloth, a kettle (to contain the creative process), it is level, it is a cow with a calf, a large wagon, form and the multitude. . . ."[2] (The opposite of the oneness of Yang.)

Technology is penetrating. Our patient is receptive.

Relationship requires receptivity from physician and patient and receptivity is the yin—the feminine principle. Technology and the other impersonal aspects of medicine, business, and politics belong to yang, the masculine principle. I agree so much with what you say, that the necessity now is a balance in our valuing equally each aspect, and yes, there should be no warring when we try to achieve balance.

War implies power, one over the other.

Balance implies union, and love, if you will allow.

The great danger that I find in modern medical practice is the apparent continued devaluation of the yin component and the overvaluation of yang; of advances in technologies, ever so fascinating and glamorous, and with impressive price tags escalating ever higher. The toys of medicine, I call them! Toys of the ever-searching scientific mind not always in touch with its yin principle, which at times loses itself in the mysteries that abound in our universe and often, carrying along the earthbound clinician, working in the real world of flesh, psyche, and disease, into that stratosphere of ideology and exquisite design.

Yes, we need a balance here and everywhere I look, it seems, in our present day world. Much of the disunity in which we abound is due very much to modern societies further devaluing yin, our mysterious mother, without whom there would be no life at all.

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Recent Trends in Lung and Breast Cancer Mortality in California Women

To THE EDITOR: We would like to bring the following information to the attention of your readers.

Cancer is the second leading cause of death in California and the United States. In 1986, the last year for which there are complete state statistics, 46,412 people died of cancer in California. That equates to 23% of all deaths or an average of 127 deaths per day.

Lung cancer has long been the leading cause of cancer death for men in California and the nation; however, it has been the leading cause of cancer death for women in California only since 1983, when it surpassed breast cancer for the first time. California was one of the first states in which lung cancer became the leading cause of cancer death in women.

In 1986, there were 4,633 deaths due to lung cancer in California women (or approximately 13 deaths per day), and 4,107 breast cancer deaths (or about 11 deaths per day).

Lung cancer deaths among California women in 1986

exceeded breast cancer by an even larger amount than in previous years. In 1983, the death rate for lung cancer was 31.0 per 100,000 women; in 1986, this rate had increased to 34.0. Conversely, breast cancer deaths, which had long been the leading cause of cancer deaths for women, decreased from 30.9 in 1983 to 30.2 in 1986.

Since 1970, death rates for breast cancer have shown relatively little change, varying from a low of 28.7 deaths per 100,000 women in 1970 to a high of 30.9 in both 1982 and 1983. In contrast, death rates for lung cancer in women have more than doubled, rising from 14.4 per 100,000 in 1970 to 34.0 in 1986.

The most recent national data showed that the lung cancer death rate had increased for women, going from 29.8 per 100,000 women in 1984 to 31.6 in 1985. And while the 1985 national lung cancer death rate for women was lower than the breast cancer rate, the continued increase in lung cancer among women will probably make it the leading cause of cancer deaths nationally, in both men and women, in 1986, even though the national breast cancer rate seems to be increasing, rising from 32.5 deaths per 100,000 women in 1984 to 32.7 in 1985.

Unlike what has occurred in California, where lung cancer death rates for men are beginning a downward trend, the national rate of lung cancer in men continues to increase. The US lung cancer death rate per 100,000 men was 70.6 in 1983, 71.7 in 1984, and 72.2 in 1985.

It is well established that the major cause of lung cancer is cigarette smoking—for both men and women. Since the Surgeon General's report on smoking in 1965, the percentage of adult smokers in California and elsewhere has gradually decreased. For example, data from a statewide survey of California adults in 1979 showed that 34.5% of men and 30.2% of women smoked cigarettes, while in 1987, a similar statewide survey of adults found that 22.5% of men and 20.1% of women smoked.

Not unexpectedly, the number of deaths due to lung cancer in women continues to rise consistent with the overall increased number of women smokers in the past two decades and the long latency of tobacco-induced cancer. If the number of women who smoke continues to decline, as has occurred in very recent years, then this will be mirrored by a commensurate decrease in the rate of lung cancer among women, similar to what is now being seen among men in California. Unfortunately, though, such a change is not likely to occur for several years, and the lung cancer rate among women will probably continue to climb for some time.

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Excisional Biopsy for the Suspicious Breast Mass

I READ WITH INTEREST "The Lumpy Breast" in the August issue.[1] The importance of the issues discussed cannot be overemphasized.

Perhaps it is my surgical background that makes me take exception to one part of the schematic for "the evaluation of a suspicious breast mass." The authors place an undue reliance on the result of the fine needle aspiration (FNA) and mammogram when they document a potential 30% false-negative rate on the mammogram and a possible 5% false-negative rate on FNA.

I think that a suspicious or dominant mass with a benign cytologic examination, regardless of the mammogram result, must be pursued with excisional biopsy. In my opinion, the "careful clinical follow-up every six months" of such a mass, as suggested in the paper, is contrary to the best interests of the patient.

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Seminars in Health Care Delivery

Opportunities for Health Promotion and Disease Prevention in the Clinical Setting

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Advances in medicine offer unprecedented opportunities to improve health. New diagnostic, care, and treatment approaches are having a tremendous impact; yet, the leading causes of morbidity and mortality in the United States are intimately linked to preventable factors such as smoking, improper nutrition, alcohol misuse, lack of exercise, and maladaptive behaviors. Compelling evidence indicates that reducing risk factors yields substantial overall health benefits and saves lives. Prevention efforts can be applied effectively at many points in a disease process, and clinical medicine has a significant role. Nonetheless, a number of barriers may interfere. These include physician education and attitudes; patient education, expectations, and motivations; and aspects of the health care delivery system itself, such as access and reimbursement. The situation has been complicated by the apparent lack of consensus on the appropriate frequency and scope of such activities.

This feature appears regularly in THE WESTERN JOURNAL OF MEDICINE. It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.

STEVEN A SCHROEDER, MD
Series' Editor

Medicine today has an unprecedented capability to improve health. Scientific advances, with new insights into human biology and disease, present exciting new prospects through both therapeutic and preventive interventions. The readiness of physicians to make use of the full range of these opportunities on behalf of their patients is less certain. Many of today's professional and economic incentives encourage physicians to place an increasing emphasis on technologic approaches to cure or alleviate disease. This perspective is fostered by tertiary medical care and medical education centers and reinforced by media reports of the miracles of modern medicine. Wondrous though progress has been, society has suffered some consequences of too narrow a focus along this dimension—consequences in the form of illness and death that ought to be entirely preventable.

Despite the vast resources—scientific, economic, and human—devoted to health care, it is a disturbing fact that close to 60% of all deaths that occur annually in the United States are premature, and an equivalently high proportion of the disability and illness could be avoided.[1] Cardiovascular disease, cancer, stroke, and injuries—the leading causes of adult death in this country, accounting for nearly 75% of deaths annually—are intimately linked to preventable risk factors (Table 1).[2,3] Many of these factors, including smoking, improper nutrition, alcohol misuse, overweight, lack of exercise, and maladaptive responses to stressful experience, can be modified by changes in personal behavior or social choices.[4] Correspondingly, new health concerns revolve around the impact of behavior and life-style on disease and how preventive measures can be effectively applied.

In fact, we are in the midst of a major transformation in the perception of health and disease. New challenges emerge for the practice of medicine as the traditional roles of physicians, hospitals, and health care settings are broadened. Concerns related to prevention, screening, and behavioral change to reduce health risk factors have not previously been at the center of practitioners' attention but are rapidly gaining in importance.

Potential Benefits of Health Promotion and Disease Prevention

There is compelling evidence that intervention to decrease risk factors yields substantial health benefits and saves lives. For example, a recent assessment by the Carter Center of Emory University (Atlanta) estimated that about 45% of cardiovascular disease deaths, 20% of cancer deaths, and more than 50% of the disabling complications of diabetes mellitus could be prevented through an improved and broadened application of existing preventive measures and risk-reducing strategies.[2] According to another evaluation, focusing on fewer than ten risk factors could potentially

(McGinnis JM, Hamburg MA: Opportunities for health promotion and disease prevention in the clinical setting. West J Med 1988 Oct; 149:468-474)

From the Office of Disease Prevention and Health Promotion, US Department of Health and Human Services (DHHS), Washington, DC (Dr McGinnis), and the National Institute of Allergy and Infectious Diseases, National Institutes of Health, US DHHS, Bethesda, Md (Dr Hamburg).

Reprint requests to J. Michael McGinnis, MD, Deputy Assistant Secretary for Health, Office of Disease Prevention and Health Promotion, US Department of Health and Human Services, 330 C St SW, Room 2132, Washington, DC 20201.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus
LDL = low-density lipoprotein

prevent between 40% and 70% of all premature deaths, a third of cases of acute disability, and two thirds of those of chronic disability.[5] While physicians cannot be held accountable for the life-style choices of a patient population, it is clear that a number of potentially life-saving opportunities are now being missed.

Clinical medicine has traditionally taught and practiced an organ-system approach to disease. Yet, heightened awareness and improved identification of risk factors contributing to the development or progression of disease may ultimately prove more valuable in attempts to combat disease. It may be helpful to briefly summarize the contributions of selected risk factors to mortality and morbidity in the country.

Tobacco Use

Cigarette smoking is the single most important preventable health problem in the United States today.[6] All told, smoking is the major cause of diseases that kill at least 350,000 Americans each year.[3] Authorities estimate that tobacco use contributes to 30% of cardiovascular disease deaths, 30% of cancer deaths, and 30% of respiratory disease deaths. More specifically, smoking is a powerful risk factor for atherosclerosis, coronary artery disease, peripheral vascular disease, and stroke.[6] Moderate smokers have a tenfold increased likelihood of lung cancer as compared with nonsmokers, while the figures for heavy smokers are even higher.[7] Smoking is associated with at least 50% of the cancers of the mouth, larynx, and esophagus and roughly 30% of kidney and pancreatic cancer.[8] It is a major cause of chronic lung disease, accounting for 80% to 90% of cases of chronic obstructive lung disease. Smokers in whom even common respiratory tract infections develop have more difficulty recovering as compared with nonsmokers.[9]

TABLE 1.—*5 Leading Causes of Death in the United States and Associated Risk Factors Commonly Encountered in Clinical Practice*

*Cause of Death**	*Risk Factors*
Cardiovascular disease	Tobacco use
	Elevated serum cholesterol
	High blood pressure
	Obesity
	Diabetes mellitus
	Sedentary life-style
Cancer	Tobacco use
	Improper diet
	Alcohol
	Occupational or environmental exposures
Cerebrovascular disease	High blood pressure
	Tobacco use
	Elevated serum cholesterol
Accidental injuries	Safety belt noncompliance
	Alcohol or substance abuse
	Reckless driving
	Occupational hazards
	Stress or fatigue
Chronic lung disease	Tobacco use
	Occupational or environmental exposures

*Adapted from National Center for Health Statistics.[3]

New research has shown that the dangers of smoking extend to include those nonsmokers passively exposed to the sidestream smoke from the cigarettes of others. Studies have shown that nonsmoking spouses of smokers suffer about twofold increased rates of lung cancer as compared with spouses of nonsmokers. Children who live with adult smokers appear to be at risk for more frequent respiratory tract illnesses.[10]

Diet and Nutrition

Diet and nutrition are clearly essential ingredients in good health, although the aggregate contribution of appropriate nutrition to promoting health and preventing disease is difficult to measure. Poor dietary patterns play a role in many of the leading causes of death and disease in this country, including cardiovascular disease, cancer, stroke, diabetes, and cirrhosis.

The most distorted dietary practice among Americans is the disproportionate emphasis on dietary fats and cholesterol—at the expense of complex carbohydrates and fiber. Over the past several decades, experimental and epidemiologic evidence has accumulated to support the role of elevated serum cholesterol levels in the development of cardiovascular disease.[11] In clinical trials there has been a decrease in disease with a reduction of serum cholesterol levels, achieved through both pharmacologic and dietary interventions.[11] Work is now underway to assess the extent to which reducing cholesterol levels actually may lead to a reversal of coronary artery disease.[12]

The Lipid Research Clinics Coronary Primary Prevention Trial, a controlled clinical trial using placebo versus a lipid-lowering resin cholestyramine, looked at middle-aged men with primary hypercholesterolemia but without clinical evidence of heart disease. The long-term results reported in 1984 showed that the cholestyramine group had significantly greater reductions in cholesterol levels and a 19% reduction in the risk for coronary artery disease.[13] Two recently completed, multicenter, randomized, controlled trials indicate that a new type of cholesterol-lowering drug, lovastatin, appears to be more effective in lowering cholesterol levels and better tolerated than cholestyramine.[14,15] Rather than binding cholesterol, lovastatin acts by inhibiting cholesterol synthesis in the liver, producing a compensatory increase in hepatic low-density-lipoprotein (LDL) receptors and an accompanying increased uptake of circulating LDL. The overall effect is that of lowering plasma LDL concentrations with a decrease in total plasma cholesterol. High-density-lipoprotein concentrations appear to increase or remain unchanged.[14,15]

Long-term studies to show the effect of the use of lovastatin on coronary artery disease have not been done. Because the drug is at least as effective in lowering cholesterol as cholestyramine, however, the use of lovastatin can be anticipated to show significant reductions in coronary artery disease mortality rates.

Despite the effectiveness of cholesterol-lowering medications, these should not replace a low-fat diet as the initial and preeminent approach to reducing cholesterol levels. Several recent clinical trials have shown that modifying dietary habits can reduce high cholesterol levels and therefore the risk for cardiovascular disease.[13] In addition to being effective, dietary modification avoids the costs, side effects, and

compliance problems of long-term drug therapy. A low-fat diet also offers many advantages beyond simply reducing the risk for coronary artery disease.

Dietary factors are implicated in the etiology of various forms of cancer, although the magnitude of the contribution is exceedingly difficult to quantify. Multiple influences are involved, including both possible causal agents such as dietary fat, nitrites, aflatoxins, and polycyclic hydrocarbons, as well as possible protective agents such as vitamins A and E (and their precursors), selenium, and dietary fiber. Following a considerable analysis of available information, Doll and Peto provided an estimate used by the National Cancer Institute that approximately 35% of cancer deaths are related to dietary factors.[8]

Dietary excess, generally reflected in excess fat and calories, is an important and not uncommon contributor to morbidity and mortality. As noted, diets high in saturated fats are associated with increased rates of coronary artery disease and other atherosclerotic diseases, as well as various forms of cancer such as those of breast, colon, and prostate.[5] At 37% of total calories, dietary fat is consumed in the United States at levels far higher than the 30% recommended by the American Heart Association or the approximately 25% found in the Japanese diet. Additionally, dietary excess contributes to the problem of obesity. An estimated nearly 23% of adult Americans are significantly overweight, defined as 120% or more of ideal weight.[16] Obesity is a contributing risk factor in a range of health problems, notably heart disease, diabetes mellitus, and musculoskeletal conditions.

Dietary deficits also are important to consider, contributing to increased disease susceptibility and decreased resistance, perinatal mortality, low-birth-weight infants, and sterility, to name a few of the associated health problems.[5]

Alcohol

While a large proportion of Americans who drink do so in moderation, an excessive use of alcohol remains an important contributor to avoidable death and disease. Surveys indicate that almost 23% of adults have consumed five or more drinks on an occasion one or more times in the preceding month, with almost one out of seven young adults reporting drinking and driving.[16]

Alcohol misuse is estimated to contribute to more than 100,000 deaths annually from a variety of causes. It is implicated in at least 3% of cancers, and excessive consumption is associated with cancers of the mouth, esophagus, larynx, and liver.[2]

Not surprisingly, the single largest contributor to chronic liver disease is excessive alcohol consumption. Conservative estimates suggest that 60% of cases of cirrhosis in the United States are caused by alcohol abuse, although many experts believe that the proportion is closer to 80% to 90%.[2]

Alcohol abuse is a considerable risk factor for accidents and injury.[17] The misuse of alcohol is felt to be involved in 40% to 50% of motor vehicle deaths and 10% to 30% of vehicular injuries each year.[2,17] Alcohol abuse, along with other substance abuse, is estimated to contribute to about 9% of fires, accidents, and violent crimes.[5]

Trauma, Accidents, and Injury

Injuries—intentional and unintentional—represent a major source of death and disability in the United States. Following cardiovascular diseases and cancer, injuries represent the next leading cause of death. Because such injuries affect a greater proportion of young people than other major health problems, they constitute the most important source of potential years of life lost or premature death. For the age group between 5 and 44, injuries, including accidents, homicides, and suicides, kill more people than all other causes combined.[5]

Motor vehicle accidents account for about half of all fatal unintentional injuries. Common and preventable risk factors linked to motor vehicle trauma and death are not using a seat belt, reckless driving, and alcohol misuse. Properly using seat belts, for example, can prevent deaths and limit injuries in as much as 60% of motor vehicle crashes.[1,18]

As mentioned, alcohol and substance abuse greatly increase the risk for both accidents and violence-related injuries.

Hypertension

High blood pressure is a risk factor for stroke, myocardial infarction, congestive heart failure, and renal disease. Controlled trials suggest that even a modestly elevated blood pressure increases the risk of cardiovascular, cerebrovascular, and renovascular disease.[19] In one analysis, hypertension was associated with 7% of all deaths.[5] As clinicians are well aware, significant improvements in blood pressure control have been achieved through both drug therapy and behavioral interventions such as dietary change, weight loss, and exercise.

Exercise

Emerging scientific evidence strongly supports the long-held notion that exercise is beneficial to health in a number of ways, including reducing the risk of cardiovascular disease; enhancing musculoskeletal integrity; improving weight control, hypertension control, and glucose tolerance; and enhancing mood and energy levels.[4] In one community-based study of cardiovascular disease, physical inactivity was estimated to account for as much as 23% of cardiovascular risk.[20] Other studies support the notion that regular exercise can reduce coronary artery disease risk significantly, even when other factors such as elevated cholesterol levels, smoking, and hypertension are controlled.[21]

Nonetheless, in 1985 less than half of the US adult population reported exercising on a regular basis, and only a quarter had done so for five years or more.[3] The current best estimate is that only about 10% to 20% of adults participate in exercise required for cardiorespiratory benefit—30 minutes of activity at least three times a week at an intensity requiring 50% maximal oxygen consumption.[22]

Stress, Social Isolation, and Bereavement

Stress and how it is dealt with appear to contribute, by as yet poorly understood mechanisms, to health and disease. Immune response and disease resistance are modified by factors related to stress.[23] Social isolation also influences health status. Interestingly, persons who live alone with relatively few social contacts seem to have a risk of mortality from all causes that is two to three times the risk for others. Several studies have also shown that the loss of a spouse exposes the bereaved spouse to a higher risk of death in the year following the death of the spouse.[4]

Although relatively few in number, it can be seen that these risk factors are responsible for a large proportion of mortality, morbidity, and health care expenditures in this country. Moreover, these risk factors generally do not act in

isolation. Rather, they tend to occur together and often act in a synergistic fashion, exacerbating their harmful effects. For example, the additive effects of smoking, elevated cholesterol levels, and hypertension are well documented: smoking doubles the risk for heart disease, while combining smoking with elevated cholesterol or hypertension increases the risk fourfold. Combining all three factors together places a person at eight times greater risk.[6] Another example is the apparent interaction between alcohol use and smoking in the etiology of certain cancers of the upper gastrointestinal tract, including cancers of the esophagus, pharynx, and larynx.[5]

A large proportion of health problems commonly encountered in clinical practice are associated with these same risk factors.

Acquired Immunodeficiency Syndrome

Clinicians today face a new and growing health challenge, the acquired immunodeficiency syndrome (AIDS). This disease process, caused by infection with the human immunodeficiency virus (HIV), represents one of the most pressing public health problems in this country and around the world. As there is presently no known vaccine or cure for the disease, prevention strategies are the most powerful tools for controlling the spread of HIV infection.[24]

There is a wide spectrum of HIV infection, ranging from asymptomatic HIV antibody positive to full-blown AIDS. AIDS represents the terminal and, to date, always fatal stage of HIV infection. The predominant modes of HIV transmission are sexual contact with an infected person, infected intravenous equipment, contaminated blood and blood products, and from an infected mother to her infant perinatally.[25]

The number of persons actually infected with HIV is difficult to determine adequately but has been variously estimated.[25] Currently in the United States, roughly 1.5 million people are thought to be infected, although many remain totally without symptoms. Over the period since 1981 when the first cases of the disease were reported to the Centers for Disease Control (CDC) of the United States Public Health Service through the end of December 1987, close to 50,000 of those infected were reported to suffer from AIDS, and almost 28,000 had died.[26] Given the estimate that AIDS develops in roughly 20% to 30% of infected persons within five years of infection, it is projected that there will be at least 270,000 cumulative cases of AIDS by 1991.[27]

The AIDS crisis has focused renewed attention on physicians' multiple roles as scientists, objective clinicians, compassionate care givers, and public health advocates. Physicians and other health care providers have a particularly vital part to play in preventing and controlling HIV infection. Beyond the appropriate care and treatment of those with known AIDS, persons who may be infected need to be identified, counseled, and informed about risks to themselves and others. When patients are seropositive, physicians should counsel them regarding responsible behavior to prevent the spread of HIV, along with health strategies to protect their compromised immune system insofar as possible and the advisability of notifying sexual contacts, past (five to ten years) and present. Those who are not infected need to be made aware of what are high-risk behaviors and how to change their behavior to minimize their risk of infection (Centers for Disease Control, United States Immunization Survey, US Department of Health, Education, and Welfare, unpublished data, 1979).

As the medical profession strives to reduce the burden of illness for this disease and many others, preventive measures and health promotion techniques must receive increased emphasis in the clinical domain.

Levels of Prevention

Prevention strategies are often classified according to where in the natural history of the disease the intervention is made. The concepts of primary, secondary, and tertiary prevention are applied.[28] These so-called levels of prevention provide a useful framework to guide how and when meaningful interventions can be made. Complications often do arise, however, because many conditions have multiple etiologic and contributing factors and certain conditions may also be risk factors for other outcomes.

Primary prevention equips healthy persons with the means of preventing the occurrence of disease or disability. Examples of primary interventions include immunizations and general health information, education, and counseling programs about health risk behaviors.

Secondary prevention intercedes to detect asymptomatic or early disease. The goal, at best, is to reverse the disease and, at a minimum, to reduce complications and the progression of disease. Controlling high blood pressure may be the best example of secondary prevention.

Finally, tertiary prevention seeks to control the progress of disease in persons with symptomatic illness or injury. These activities have the potential to effectively reduce the burden of death and disability from chronic conditions.

Across all these levels of prevention, clinical medicine has an important role to play. Most medical professionals are involved predominantly in secondary and tertiary preventive care. The focus is on restoring health after it is lost. On the other hand, in some specialty areas, health maintenance has long been an important part of practice. For example, pediatrics has traditionally had a strong focus on prevention and health promotion. Central components of pediatric care have included immunizations against disease, well-baby-care visits, an emphasis on dietary and behavioral influences on health, and working closely with parents to foster healthy growth and development. Similarly, for several decades now, obstetricians have placed considerable emphasis on careful health monitoring during pregnancy. The encouragement of appropriate health promotion regimens and periodic assessments of maternal and infant health during pregnancy has led to notable declines in perinatal morbidity and mortality.[3]

There is encouraging evidence that most physicians recognize the importance of health promotion and risk reduction.[29] For some, health promotion is equated with a fairly narrow set of activities including immunization and screening for asymptomatic disease, but many physicians are receptive to the notion of providing broader health counseling and preventive services. Nonetheless, clear discrepancies exist between the acknowledged importance of prevention and providing appropriate preventive care.

Poor compliance to preventive care standards and an underemphasis on the role of health promotion have been noted in private practice settings, university-based practices, and among house staff and residents training in primary care. A number of studies have documented a low use of preventive procedures by physicians, both by self-report and by examining patterns of performance in practice.[30-33] Interestingly, one recent study indicated a tendency for some physicians to

overestimate the amount of preventive care that they actually provided.[32]

Several sources indicate that the delivery of even the most fundamental preventive services falls short of recommended practices. Data reported from the CDC indicated that perhaps as many as half to three quarters of 1-year-old children had not received a complete set of immunizations.[31] This general finding was supported by a study that documented that only 45% of infants received appropriate immunization for diphtheria, pertussis, tetanus, and polio (CDC, unpublished data, 1979).

Barriers to Implementation

What, then, are some of the barriers that interfere with the appropriate provision of health care services? Perhaps more than other aspects of medicine, health promotion and disease prevention rely on the coordinated participation of patient and physician, as well as a health care system capable of supporting that effort. Obstacles can occur at many places along the spectrum.

Physician Barriers

Many factors may influence physicians' attitudes toward prevention and health promotion, leading to the noted failure to provide adequate preventive services. Many of the reasons are readily apparent to practitioners. Medical training and practice are traditionally oriented toward recognizing and treating disease. Medical education affords little attention to preventive health practices. In many instances, physicians may not be sufficiently knowledgeable about specific health practices, potential benefits, or existing standards for preventive care. This problem is exacerbated by an apparent lack of consensus on recommendations or disagreements with indications for screening. Even with respect to preventive services of acknowledged value, physicians may cite lack of time, forgetfulness, or inadequate facilities as reasons for not performing these activities.[32,34]

Many physicians feel uncomfortable in dealing with health problems that are primarily behavior related such as smoking or weight reduction.[35] Health education and counseling may be perceived as peripheral to the practice of medicine, especially because they do not require the services of a trained physician. Furthermore, doubts about the effectiveness of such counseling may often lead to silence about important health concerns. For example, several studies have found that only 25% to 30% of current smokers report receiving a physician's advice to quit, although a national poll indicates that 70% of moderate to heavy smokers say they would quit if their physicians urged them to do so.[9] It has been suggested that physicians who recommend cessation to patients who smoke can increase 12-month smoking cessation rates from 1% to 5%.[9] Behavior change is a complex, difficult, and often slow process. The maintenance required for optimal outcomes is even harder to achieve. Even with an intensive commitment by physicians to foster prevention and health promotion, the reward principally must take the form of anticipated reductions in morbidity and mortality—not the more immediate evidence of benefit and the gratification experienced with diagnosis, treatment, and cure.

Patient Barriers

A range of factors may influence a patient in seeking or accepting health promotion and preventive services. Patients may lack knowledge of the options and potential benefits entailed in preventive care. They may be reluctant to receive certain screening and assessments based on denial or fears of discovering a dreaded disease. Reluctance to receive a procedure may also arise from concerns of discomfort, embarrassment, or inconvenience. Patients may be aware of poor health habits but resent interference by their physicians, or they may be reluctant, uncooperative, or feel unable to undertake difficult behavioral changes. Many patients seeking a physician's care simply want and expect care and treatment for acute conditions, not behavioral advice.

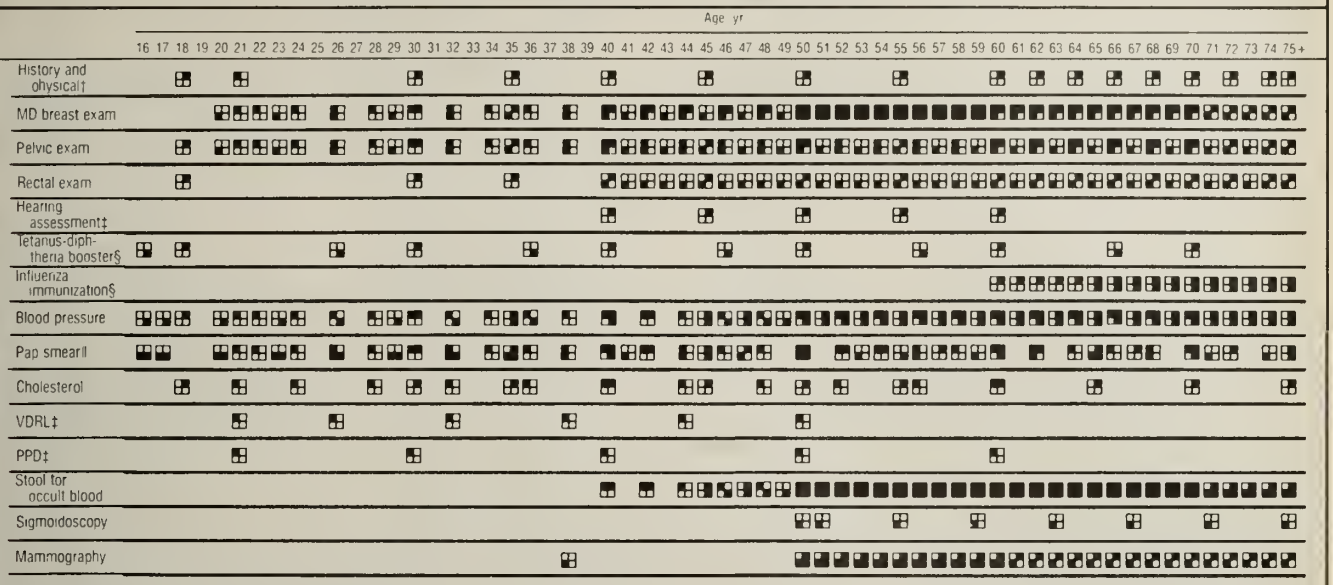
Health Care Delivery System

It is often suggested that the major obstacle to optimally providing preventive services derives from the organization of the health care delivery system. Medical insurance emphasizes "acute care" over prevention and generally reimburses poorly or not at all for basic forms of prevention such as counseling, screening, and routine examination. Third-party payers are beginning to explore reimbursement mechanisms for preventive services as an approach to improving client health and reducing costs. Project INSURE, for example, is presently evaluating a health care delivery system in which primary care physicians are reimbursed for cognitive services such as counseling and education.[36] A recently published study of enrollees in the Rand Health Insurance Experiment indicated, however, that an adequate reimbursement for preventive services did not ensure that physicians provided the recommended services.[30] This is reinforced by experience in other countries such as Great Britain, where despite minimal or no charge for preventive services, they are in fact delivered at far lower rates than in the United States.[37]

Although payment barriers clearly are important, there are many other disincentives to preventive care within the health care system.[34] Generally, physical access to services is no longer a major obstacle for low income and minority populations in this country. The types of services used by these populations, however, are not the types most conducive to the delivery of preventive services. Studies have indicated a twofold to threefold increased likelihood that such persons will use hospital and emergency department settings as their primary source of care rather than comprehensive regular and continuing care settings.[38] For this reason and perhaps others, minorities are less likely to have diagnostic tests for various health problems, particularly those related to cancer.

In addition to problems of economic and physical access to preventive services, a major obstacle exists simply in the traditional structure of the medical care encounter. The reality of modern practice is that physician-patient visits are time limited and problem oriented. As noted earlier, expectations generally are held by both physicians and patients that the medical encounter will focus on the acute or chronic problem that prompted the visit. Attempts to modify potentially health-damaging behavior or identify evidence of asymptomatic disease may have greater long-term effects in terms of a patient's health outcome, but expressed satisfaction from the visit may be lower for both patient and physician. Trends suggest, however, that the perception of the health care system as the source of disease treatment and care has been expanding to include concepts of health promotion and disease prevention.[39]

TABLE 2.—*Summary of Recommendations for Periodic Health Examination**



F	B & S
ACS	CTF

F Frame and Carlson[43]
B & S Breslow and Somers[44]
ACS American Cancer Society[40]
CTF Canadian Task Force on the Periodic Health Examination[42]

PPD=purified protein derivative

*Summary of recommendations of four major studies. Adapted from the American College of Physicians guide.[41] A blackened square indicates that a study has considered the maneuver and recommended it. Squares left empty do not necessarily indicate that the study considered but did not recommend the maneuver. This example is provided for illustrative purposes. An updated, comprehensive periodic health examination is currently under development by the Office of Disease Prevention and Health Promotion based on the work of the US Preventive Services Task Force. This guide will be published in late 1988.

†Counseling about risk factors should be an important component, particularly concerning tobacco use, diet, exercise, and injury prevention.

‡Canadian Task Force recommends that this be done on the basis of clinical judgment.

§At first visit physicians should check past immunization history per Centers for Disease Control recommendations for rubella, mumps, poliomyelitis, diphtheria/tetanus toxoids, and pertussis.

‖If sexually active.

Screening and Periodic Health Examination

Given this background, what preventive measures and health promotion techniques should be encouraged in clinical practice? The appropriate frequency and scope of such activities have produced considerable confusion and debate.[40] The concept of periodic health evaluations is not new. In the 1920s, the American Medical Association endorsed the annual checkup as conferring long-term health benefits.[39] Over the ensuing years, various individuals, professional groups, and voluntary organizations have issued recommendations concerning the components and frequency of preventive interventions. For many years the American Cancer Society and the American Heart Association have played a prominent role in providing health screening recommendations.[39,40]

Almost a decade ago the Canadian Department of National Health and Welfare established a task force on the periodic health examination that presented guidelines for health screening based on an evaluation of the proven effectiveness of preventive measures.[42] In this landmark effort, recommendations were made on more than 70 conditions. An updated set of recommendations was published in 1984. This document reflected clearly the underlying premise that any patient visit is an opportunity for preventive care and emphasized the importance of counseling for primary prevention and case findings for secondary prevention. A summary of representative recommendations from various sources is provided in Table 2.[40-44]

Progress in biomedical and behavioral sciences will enable new screening, diagnostic, and therapeutic modalities to augment capacities for preventive interventions. New knowledge about the efficacy of prevention will increase the ability of clinicians to adopt preventive measures as an integral part of their practice. There is tremendous potential for improvements in health through the application of what we already know about prevention. Simply a renewed focus on risk factors could dramatically alter the patterns of death, disability, and disease in this country: some 350,000 deaths per year attributed to smoking could be prevented; dietary changes could substantially reduce diseases of the cardiovascular system and certain cancers; modifying alcohol and substance abuse would reduce the extraordinary human and economic costs presently exacted. Even the specter of AIDS could be lessened if we could truly implement strategies for risk reduction and prevention. If the gains possible are indeed to be accomplished, physicians must be leaders not only in the battle against disease but in the cause of good health.

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Health Care Delivery

Managing Low Back Pain—A Comparison of the Beliefs and Behaviors of Family Physicians and Chiropractors

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Random samples of 605 family physicians and 299 chiropractors in Washington were surveyed to determine their beliefs about back pain and how they would respond to three hypothetic patients with back pain. With 79% of the family physicians and 70% of the chiropractors responding, family physicians and chiropractors differed greatly not only in their technical approaches to back pain—such as drug therapy versus spinal manipulation—but also in their underlying beliefs and attitudes. Family physicians think that most back pain is caused by muscle strain, that lumbosacral radiographs are rarely useful, that appropriate therapy does not depend on a precise diagnosis, and that back pain will usually resolve within a few weeks without professional help. Family physicians were more likely than chiropractors to feel frustrated by patients with back pain, less likely to think they can help patients prevent future episodes of back pain, and less confident that their patients are satisfied with their care. Studies are needed to determine whether the different perspectives of family physicians and chiropractors are associated with differences in the costs and outcomes of care.

(Cherkin DC, MacCornack FA, Berg AO: Managing low back pain—A comparison of the beliefs and behaviors of family physicians and chiropractors. West J Med 1988 Oct; 149:475-480)

Back pain is one of the most common and costly health problems affecting the populations of industrialized nations. Swedish studies suggest that as many as 80% of adults will experience back pain during their lifetimes[1] and that 40% to 50% of adults experience back pain each year.[2] An estimated $5 billion is spent annually in the United States on the diagnosis and treatment of back pain, and an additional $14 billion is consumed in lost productivity, disability payments, and lawsuits.[3]

According to the 1980 National Medical Care Utilization and Expenditure Study, 40% of Americans with chronic back pain sought care for their back pain during 1980 from doctors of medicine or osteopathy and 30% sought care from chiropractors.[4] Because persons receiving back care from chiropractors made more visits than those receiving care from allopathic and osteopathic physicians (means of 8.2 and 2.8 visits, respectively), almost two thirds of all visits for back pain were to chiropractors. Despite the prominent role that chiropractors play in caring for patients with back pain, there is little information in the medical literature about how chiropractors actually manage patients with back pain, the efficacy of chiropractic therapy, or the relative cost-effectiveness of chiropractic care versus allopathic or osteopathic care for this problem.

Because of concerns about the costs and quality of care given patients with back pain, an effort was made to learn how family physicians and chiropractors provide care for patients with back pain and how patients respond to the care they receive from these practitioners. We compare the beliefs and attitudes about back pain of family physicians and chiropractors and their clinical responses to patients with back pain.

Methods

Provider Samples

The physician sample included all 181 family physicians employed by the largest health maintenance organization (HMO) in the state of Washington and a 50% random sample (424) of the 847 non-HMO members of the Washington Academy of Family Physicians. The higher sampling rate of HMO physicians was required to ensure an adequate sample size for a second HMO-based study of low back pain comparing physician and patient responses. The HMO does not employ chiropractors, though about a third of its 320,000 enrollees have insurance coverage for up to $200 of self-referred chiropractic services per year. Chiropractors were selected by taking a 50% random sample of the 642 members of the Washington State Chiropractic Association residing in the geographic area served by the HMO—that is, the Puget Sound area.

Survey Instruments

A two-stage process was followed in constructing the survey instruments used to gather information from the providers. First, separate groups of family physicians and chiropractors were assembled for discussions of how they

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managed patients with back pain. This process helped us identify the range of provider beliefs, attitudes, and behaviors associated with managing back pain. Using the discussion group information as a guide, we then constructed and pilot-tested questionnaires designed to determine the prevalence of the specific beliefs and behaviors that had been identified.

The questionnaires included items concerning provider characteristics—such as age, sex, years in practice, adequacy of training to manage back pain, and personal experience with back pain—provider beliefs and attitudes about managing back pain, and attitudes about patients with back pain. In addition, three clinical vignettes were included that asked providers what tests, therapies, and follow-up they would order for three different types of patients with back pain. Providers were also asked how confident and comfortable they would feel when managing each type of patient. These vignettes were chosen to cover a wide range of types of patients with back pain that are frequently seen in primary care settings. For each vignette, providers were asked to indicate their most likely response on the first visit with these patients. The vignettes were as follows:

Patient 1. A 37-year-old woman sees you with her first episode of low back pain. It was of sudden onset yesterday when she bent over to pick up her 3-year-old daughter. The pain is constant and she is having difficulty performing her usual activities. She has some muscle tenderness in the lower back, but the neurologic examination is normal.

Patient 2. A 44-year-old man sees you for the first time, complaining of mild low back pain. He has been seen by other physicians over a period of years for recurrent low back pain dating to an injury ten years ago while working in a warehouse. He says that previous physicians were unable to find a cause for the pain. He cannot pinpoint when the pain started this time but thinks it might have been related to working on his roof a week ago. He has no other symptoms and his general and neurologic examinations are unremarkable.

Patient 3. A 52-year-old man sees you the day after a minor automobile accident. Although he felt well initially, he was unable to sleep last night because of increasing pain in the lower back and sciatica on the left side. On examination the ankle reflex is depressed and straight-leg raising is positive.

The questionnaires sent to family physicians and chiropractors were similar except for differences in the range of specific response options for the clinical vignettes. For example, because chiropractors cannot prescribe medications, they were not asked questions about drug therapy. Chiropractors were also not specifically asked if they would do laboratory tests for their patients or if they would refer patients for physical therapy but were given an opportunity to specify "other" tests or therapies they would order. Fewer than 4% of chiropractors indicated they would order laboratory tests or physical therapy referrals on the first visit for any of the three patients. These estimates, however, might be lower than would have been found had these items been specifically listed on the questionnaire.

Response Rates

After three mailings, usable responses were received from 79% (476/605) of the family physicians. After excluding 22 chiropractors who were not in practice or whose addresses were no longer valid, the adjusted response rate for chiropractors was 70% (208/299).

Statistical Tests

Even though non-HMO family physicians were sampled at half the rate as HMO family physicians, responses by HMO and non-HMO family physicians were given equal weights in the analyses to avoid confusion about the meaning of "weighted" estimates and the statistical problems associated with calculating variance estimates for weighted samples. None of the conclusions reached in this study would be different had weighted estimates been used, as the responses of the HMO and non-HMO physicians were generally similar. Student's t test was used to compare differences between means, and the χ^2 test with continuity correction was used to compare differences in responses to dichotomous variables. The conventional criterion of statistical significance ($\alpha = .05$) was used. Due to the large sample sizes, all of the differences that were clinically important were statistically significant.

Results

Provider Characteristics

There were significant differences between the family physicians and chiropractors studied for all of the provider characteristics examined, although the differences were not large for age, sex, and years in practice (Table 1). However, 42% of family physicians felt they had been poorly trained to manage low back pain when they first entered practice, triple the percentage for chiropractors. While more than three quarters of the family physicians reported having personally had low back pain, back pain was an almost universal experience among chiropractors. Of the family physicians, 77% had completed at least two years of residency training.

Family physicians and chiropractors were also significantly different in terms of their fundamental practice style philosophies (Table 1). While more than 40% of the family physicians claimed to emphasize the "art of medicine over the science of medicine" and to "often deliberately take advantage of the placebo effect" to help their patients, few chiropractors claimed to emphasize the "art of chiropractic over the science of chiropractic," and virtually all said they did not deliberately use the placebo effect. Family physicians were also more likely to admit discomfort with clinical situations that involved a high degree of uncertainty, although the difference between the two types of providers, while statistically significant, was not large.

Patient Vignettes—Tests

Lumbosacral radiographs were ordered by almost all chiropractors on the first visits with all three patients (Table 2). In contrast, the percentage of family physicians who would

TABLE 1.—*Provider Characteristics of Family Physicians and Chiropractors Included in the Study**†

Characteristics	*Family Physicians*	*Chiropractors*
Age, mean years	43.6	41.5
Duration in practice, mean years	13.4	11.6
Male, %	84	90
Felt poorly prepared to manage back pain when first entered practice, %	42	15
Have had low back pain, %	78	97
Tend to emphasize art of medicine/chiropractic over science, %	43	11
Often deliberately take advantage of the placebo effect to help patients feel better, %	43	3
Uncomfortable with clinical situations involving high degree of uncertainty, %	45	36

*Due to missing information for some items, sample sizes range from 466 to 473 for family physicians and from 204 to 206 for chiropractors.

†All differences between providers are statistically significant ($P < .05$).

order a radiograph varied by patient, ranging from 10% for the woman with the lifting injury (patient 1) to almost 93% for the man with sciatica (patient 3). In addition, 10% to 22% of chiropractors noted they would also order other types of radiographs (primarily cervical and full-spine radiographs) for the three patients (Table 2). In all, 5% of chiropractors and 6% of family physicians indicated they would order a computed tomographic scan for the patient with sciatica.

About a quarter of family physicians would order urinalysis and the measurement of the sedimentation rate for the patient with a vague onset of pain, and a similar proportion would do a urinalysis for the patient with sciatica (Table 2). Smaller proportions of family physicians indicated they would do a complete blood count. Only about 1% of the chiropractors indicated a desire for a laboratory test. Fewer than 3% of providers said they would order any other type of test for any of the three patients.

It should be noted that some of the chiropractors expressed discomfort with the limited amount of information available on each patient, and roughly 20% made a point of noting on the questionnaires that they would do range-of-motion, palpation, neurologic, orthopedic, or chiropractic examinations as part of their assessment of the patients. In contrast, similar concerns and comments were made by only about 1% of family physicians. In addition, 22% of family physicians and 12% of chiropractors noted a desire to review the old medical records of the patient with a long history and vague onset of pain (patient 2).

TABLE 2.—*Percentages of Providers Ordering Tests During First Visit With Hypothetic Patients**†

Tests	*Patient 1*	*Patient 2*	*Patient 3*
Lumbosacral radiograph, %			
Family physicians	10	49	93
Chiropractors	92	93	95
Other plain radiographs, %			
Family physicians‡	0	0	0
Chiropractors‡	10	15	22
Urinalysis, %			
Family physicians	11	23	27
Chiropractors‡	1	1	0
Sedimentation rate, %			
Family physicians	2	27	8
Chiropractors‡	0	1	0
Complete blood count, %			
Family physicians	4	16	13
Chiropractors‡	0	1	0

*Patient 1: a 37-year-old woman with a lifting injury has disabling back pain; patient 2: a 44-year-old man has a vague onset of mild symptoms; patient 3: a 52-year-old man has sciatica after a car accident.

†Percentages are based on responses from 469 to 475 family physicians and 205 to 208 chiropractors. All differences between providers are statistically significant ($P < .05$) except for lumbosacral radiographs for patient 3.

‡Indicates write-in responses in "other" category

TABLE 3.—*Percentages of Providers Ordering Nondrug Therapies During First Visit With Hypothetic Patients**†

Nondrug Therapy	*Patient 1*	*Patient 2*	*Patient 3*
Bed rest, %			
Family physicians	52 (3.1)	18 (3.8)	86 (5.0)
Chiropractors	30 (2.7)	8 (2.5)	51 (4.4)
Spinal manipulation, %			
Family physicians	5	2	2
Chiropractors	92	86	76
Ice/heat, %			
Family physicians	84	60	71
Chiropractors	91	60	88
Exercises, %			
Family physicians	29	50	9
Chiropractors	19	43	11
Physical therapy, %			
Family physicians	13	49	21
Chiropractors‡	1	3	3

*Patient 1: a 37-year-old woman with a lifting injury has disabling back pain; patient 2: a 44-year-old man has a vague onset of mild symptoms; patient 3: a 52-year-old man has sciatica after a car accident. Percentages are based on responses from 472 to 475 family physicians and 203 to 207 chiropractors.

†The numbers in parentheses indicate the mean number of days of bed rest ordered for patients prescribed bed rest. Differences in mean number of days of bed rest between providers were statistically significant ($P < .05$) only for patient 2. All other differences between providers were statistically significant except for ice/heat therapy for patient 2 and exercise therapy for patients 2 and 3.

‡Indicates write-in responses in "other" category.

Patient Vignettes—Treatments

Family physicians were about twice as likely as chiropractors to prescribe bed rest for all three of the patients (Table 3). Among providers who prescribed bed rest, family physicians did so for a longer period of time than did chiropractors for all three patients, although the difference was statistically significant only for patient 2. Although spinal manipulation was ordered by about 90% of chiropractors for the patients without sciatica and by more than three fourths of chiropractors for the patient with sciatica, it was rarely ordered by family physicians. There were no significant differences in the proportions of family physicians and chiropractors who indicated that they would prescribe heat or ice therapy for patient 2 or in the proportions who said they would prescribe exercises for patients 2 or 3. Finally, while family physicians would refer significant proportions of their patients for physical therapy, this was rarely recommended after the first visit by chiropractors. Because 6% of chiropractors commented that they could not respond to questions concerning therapy until they had seen the results of the radiographs, the percentages for chiropractors in Table 3 might be slightly underestimated.

Two other types of responses were written in by at least 5% of providers. Depending on the patient, between 4% and 11% of chiropractors said they would prescribe orthopedic supports, whereas this therapy was never mentioned by family physicians. For the patient with sciatica, 10% of family physicians and 16% of chiropractors noted that they would consult a specialist, such as an orthopedic surgeon, a neurosurgeon, or a neurologist.

Because chiropractors cannot prescribe medications, specific questions about drug therapy were asked only of family physicians. The percentage of family physicians who said they would prescribe drugs for each of the three patients ranged from 82% to 90% for anti-inflammatory drugs, 21% to 76% for analgesics, 30% to 50% for muscle relaxants, and 1% to 6% for sedatives. None of the chiropractors indicated they would recommend even nonprescription drug therapy such as aspirin for the patients.

Patient Vignettes—Follow-up Visits

More than 90% of chiropractors said they would ask the three patients to schedule a follow-up visit at the end of their visit, and 9% said they would also call patients at home the evening of the first visit. Family physicians were as likely as chiropractors to schedule a return visit for the patient with sciatica, but only 34% would do so for the woman with the

lifting injury, and only 71% would do so for the man with the vague onset of symptoms. These differences between providers were statistically significant.

Patient Vignettes—Confidence and Comfort

Almost all chiropractors felt confident that they would be able to "greatly" or "moderately" affect the rate of recovery of all three patients (Table 4). This contrasts sharply with the responses of family physicians, many of whom felt that they would have little or no effect on the rate of recovery of the woman with the lifting injury and of the man with the vague onset of pain. Almost three quarters of the family physicians, however, felt they could speed the rate of recovery of the man with sciatica. Chiropractors were also significantly more likely than family physicians to claim to feel comfortable managing the three patients (Table 4).

Provider Beliefs and Attitudes

The beliefs of family physicians and chiropractors concerning the cause, diagnosis, prognosis, treatment, and prevention of low back pain were consistently different. Family physicians attributed the largest share of back pain to muscle strain while chiropractors thought that vertebral subluxations were the principal underlying cause of most back pain (Table 5). Almost 15% of chiropractors did not respond to this question, many of whom noted that it was not possible to identify a single cause since multiple causes existed simultaneously as a "vertebral subluxation complex."

In contrast to chiropractors, most family physicians disagreed that a precise diagnosis was a prerequisite for appropriate therapy for most low back pain and agreed that radiographs were rarely useful (Table 6). Family physicians were much more likely than chiropractors to think that there was nothing physically wrong with many patients with low back pain, though the proportion of providers holding this belief was low in both groups.

Almost 90% of family physicians but fewer than a third of chiropractors think that most low back pain will resolve itself within a few weeks without professional help (Table 6). Despite this widespread belief among family physicians, less than half said that they assured patients with low back pain that the pain would go away within a few weeks. Several chiropractors noted that although pain will often resolve without help, it will often return if the underlying problem is not addressed.

A majority of both family physicians and chiropractors agreed that effective therapies were available for most patients with low back pain (Table 7). The fact that almost 60% of the family physicians agreed that the most important thing was to make patients comfortable while nature took its course suggests that the therapies many of the family physicians considered to be effective were probably bed rest and medication. The great majority of chiropractors rejected the notion that making patients comfortable was of primary importance, presumably because they believed they could provide a therapy—that is, manipulation—that addressed the problem, not just its symptoms. Almost all chiropractors but less than 60% of family physicians thought that they could do

TABLE 4.—*Confidence in Ability to Affect Course of Illness and Comfort Dealing With 3 Hypothetic Patients With Back Pain**†

Confidence or Comfort Level	*Patient 1*	*Patient 2*	*Patient 3*
Believe able to moderately or greatly affect patient's rate of recovery, %			
Family physicians	54	23	74
Chiropractors	100	98	97
Very comfortable dealing with this type of patient, %			
Family physicians	78	33	43
Chiropractors	98	90	86

*Patient 1: a 37-year-old woman with a lifting injury has disabling back pain; patient 2: a 44-year-old man has a vague onset of mild symptoms; patient 3: a 52-year-old man has sciatica after a car accident. Percentages are based on responses from 467 to 475 family physicians and 197 to 208 chiropractors.

†All differences between providers are statistically significant.

TABLE 5.—*Principal Underlying Cause of Low Back Pain**

Cause of Back Pain	*Family Physicians, N=454, %*	*Chiropractors, N=178, %*
Muscle strain	47	14
Vertebral subluxation	2	55
Facet joint syndrome†	9	10
Disc problem	12	9
Spinal arthritis	14	7
Psychosomatic	8	2
Other, unknown	8	4
Total	100	100

*Estimated mean percentage of patients.

†Only cause of pain for which differences in estimates of family physicians and chiropractors were not statistically significant.

TABLE 6.—*Beliefs Concerning the Diagnosis and Prognosis of Back Pain (percentage agreeing with statement)**

Belief	*Family Physicians, %*	*Chiropractors, %*
Appropriate therapy for most low back pain requires a precise diagnosis	31	91
X-ray films are rarely useful in the assessment of low back pain	67	6
There is nothing physically wrong with many patients who complain of low back pain	19	3
Most low back pain will resolve itself within a few weeks without professional help	88	28
I assure patients with low back pain that their pain will go away within a few weeks	46	33

*Percentages are based on responses from 467 to 475 family physicians and 196 to 206 chiropractors. All differences between providers were statistically significant ($P < .05$).

TABLE 7.—*Beliefs Concerning Therapy and Prevention (percentage agreeing with statement)**

Belief	*Family Physicians, %*	*Chiropractors, %*
Effective therapeutic interventions are available for most patients with low back pain	71	87
The most important thing to do for patients with low back pain is to make them comfortable while nature takes its course	58	14
Doctors [MD or DC] can do a lot to prevent patients with acute back pain from developing chronic back pain	57	98

*Percentages are based on responses from 472 to 476 family physicians and 200 to 205 chiropractors. All differences between providers are statistically significant.

TABLE 8.—*Comfort Managing Back Pain and Perceived Patient Satisfaction (percentage agreeing with statement)**

Belief	*Family Physicians, %*	*Chiropractors, %*
I am very comfortable managing patients with low back pain	78	98
I often feel frustrated by patients who want me to fix them	59	23
Most of my back pain patients are very satisfied with my care for their back pain	55	99

*Percentages are based on responses from 473 to 475 family physicians and 203 to 207 chiropractors. All differences between providers are statistically significant.

a lot to prevent acute back pain from developing into chronic back pain (Table 7).

Finally, although most family physicians and virtually all chiropractors claimed to be very comfortable managing patients with low back pain, most family physicians but few chiropractors admitted that they often felt frustrated by patients with low back pain who wanted to have their backs "fixed" (Table 8). Chiropractors were also much more confident than family physicians that their patients with low back pain were satisfied with their care.

Discussion

This study has shown that family physicians and chiropractors have greatly divergent beliefs about back pain and use different clinical strategies for managing back pain. Family physicians are much less likely than chiropractors to believe that they were adequately trained to manage low back pain, that low back pain is caused by vertebral subluxations, that radiographs are important for establishing a diagnosis, that appropriate therapy requires a precise diagnosis, that patients with low back pain can be benefited by professional help, that acute back pain can be prevented from developing into chronic back pain, and that their patients are satisfied. In addition, family physicians are much more likely than chiropractors to think that there is nothing physically wrong with many patients who complain of back pain and to often feel frustrated by these patients.

According to their responses to the three patient vignettes, family physicians and chiropractors also have different practice styles that are clearly associated with their beliefs about back pain. Chiropractors virtually always order lumbosacral radiographs (and sometimes cervical or full-spine radiographs) on the first visit with a patient. In contrast, the radiograph-ordering behavior of family physicians was found to depend on the type of patient and, for some types of patients, on the individual physician's practice style. Laboratory tests are apparently rarely ordered by chiropractors but are ordered by a significant minority of family physicians for certain types of patients with back pain.

Heat or ice therapy and exercise were prescribed by roughly similar proportions of family physicians and chiropractors. Both types of providers prescribe bed rest, though family physicians do so more frequently and for longer periods of time. The main differences in therapy were that chiropractors almost always did spinal manipulation while family physicians almost always prescribed drugs and often referred patients for physical therapy. Chiropractors were also generally more likely than family physicians to ask patients to schedule follow-up visits. Finally, chiropractors were significantly more likely to think that they could hasten a patient's recovery and that their patients were satisfied with their care.

There are several limitations that should be considered when interpreting these results. First, the study was conducted in a single state. Because laws affecting chiropractic vary considerably from state to state, the differences between providers might have been more or less pronounced had this study been conducted in another state. Second, it is unclear if the types of patients seen by family physicians and chiropractors in their practices are similar. If family physicians and chiropractors in fact see very different types of patients who have back pain, they may envision the standardized patients in the vignettes differently in terms of patient and illness characteristics not specifically mentioned. Finally, the clinical vignettes were restricted to first visits with a limited range of patients, and it is not known to what extent provider responses to hypothetic patients reflect their actual behavior. In view, however, of the large and consistent differences between family physicians and chiropractors, it seems unlikely that many of the results would have been qualitatively different in the absence of these limitations.

Because chiropractors specialize in problems of the spine, it should not be surprising that they are more confident and comfortable than family physicians in managing problems such as low back pain. Because back symptoms are the third most common reason for visits to family physicians,[5] however, it is disconcerting that about half of the family physicians in Washington feel poorly prepared to manage back pain, frustrated by patients who have back pain, and limited in their ability to affect patients' rate of recovery and likelihood of developing chronic back pain. These feelings, if communicated to patients, could be detrimental to effective therapy.

There are a number of reasons, in addition to inadequate preparation, why family physicians may feel uncomfortable managing back pain. Family physicians may believe that for most patients seen in the primary care setting with back pain, the cause of the pain is unknown,[6] there are no tests available to provide a precise diagnosis, and there is no single therapy that is clearly superior to other therapies or to nature's own course.[1,7] In addition, physicians are often put in the position of passing judgment, without the benefit of objective measures, about the ability of patients to perform their usual work activities. By contrast, chiropractors believe they have the ability to provide patients with graphic evidence of the precise cause of their pain—that is, a lumbosacral radiograph—and to eliminate the cause by using a specific therapeutic maneuver—spinal manipulation—that they are confident is effective.

If primary care physicians accept that radiographs are of minimal diagnostic value for most patients and that no clearly superior therapy exists for back pain,[7] they must look for other ways in which they can help their patients. Back pain is not a scientific medical problem in the same sense as strep throat and hypertension, and its effective management probably depends more on the successful application of the art of medicine than the science of medicine. Deyo, for example, reported that patients with back pain who felt they had received an adequate explanation of their problem were more likely to be satisfied with their care regardless of whether a diagnostic test was done.[8] Future research on the primary care management of low back pain should pay greater atten-

tion to the impact of nontechnologic interventions, such as information, reassurance, caring, and legitimization, on the outcomes of care such as patient satisfaction, disability, and dependency.

In conclusion, there are large and fundamental differences between family physicians and chiropractors in terms of not only their technical approaches to back pain but also their underlying beliefs and their levels of comfort and confidence when dealing with patients with back pain. These differences between family physicians and chiropractors, if found to be associated with differences in cost or outcome, could have major implications for how this common and costly problem will be managed in the future.

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Public Health and Preventive Medicine

HIV Disease Prevention and Treatment

A Model for Local Planning

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This is one of a series of articles from western public health departments.

Since first reported in 1981, about a fourth of all cases of the acquired immunodeficiency syndrome in the United States have occurred in California. In response to the human immunodeficiency virus (HIV) epidemic, California has developed a five-point strategy consisting of epidemiologic surveillance; prevention education; the provision of medical treatment and supportive services; research; and continuous planning, evaluation, and coordination of programs. Given the size and tremendous environmental and cultural diversity of California, as well as the variable local impact of HIV disease, local jurisdictions need to develop HIV disease prevention and treatment plans specifically tailored to the circumstances of their communities. At a minimum, these plans should include central participatory planning, epidemiologic surveillance, HIV antibody testing and prevention education programs, provision for medical treatment and social support services, and coordination of financing mechanisms. We present a model for such plans.

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Since the acquired immunodeficiency syndrome (AIDS) was first reported in 1981, about a fourth of all cases in the United States have occurred in California. As of June 30, 1988, a total of 14,414 cases had been reported to the California Department of Health Services (CDHS). Of these persons, 8,378 (58%) have died.

The CDHS projects that another 35,000 cases of AIDS will occur in California by the end of 1991. It is also estimated that more than 300,000 people in California currently are infected with the human immunodeficiency virus (HIV), the causative agent of AIDS.

Based on our current understanding of the natural history of HIV infection, it must be assumed, for purposes of planning, that HIV-related illness will develop in all persons infected with the virus, and fulminant AIDS, or end-stage HIV disease, will develop in about half of these persons. Further, in the absence of a preventive vaccine, disease-arresting immunotherapy, or cure, and with none imminent, we must assume that AIDS is uniformly fatal. Education and other public health interventions continue to be the primary means of combating the HIV epidemic.

In addition to concern among the public health and medical communities, HIV disease continues to be among the top sociopolitical issues of the day, as reflected in recent public opinion polls and the nearly 150 AIDS-related pieces of legislation introduced in the California legislature in 1988. This is nearly three times more than were introduced in 1987.

It is within this context that the California Department of Health Services has prepared a document to assist local jurisdictions plan for HIV disease.[1] We think all local health departments should have a plan for the prevention and treatment of HIV disease, consistent with overall state plans and policies. We have adapted this CDHS planning document for presentation here because health care practitioners need to actively participate in the community response to the HIV epidemic. To be effective, though, they must understand the framework in which they are operating.

Factors Affecting California's Planning for HIV Disease

In the past three years, the California Department of Health Services has expended considerable effort in planning its response to the HIV epidemic and has promulgated a number of reports relating to AIDS.[1-3]

Throughout the epidemic, statewide planning for HIV disease and AIDS has been influenced by a number of factors, some of which are unique to California, while others are shared by all states. Among the factors influencing California's response, the following five are most notable.

First, California is large and diverse—a place of great

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDHS = California Department of Health Services
HIV = human immunodeficiency virus

contrasts. It is the third largest state in the nation, encompassing more than 158,000 sq mi. It is also the most populous state, with more than 28 million people. This population is not evenly distributed, however; California contains some of the most densely and most sparsely populated areas in the world. It is also the most environmentally diverse, possessing large wilderness areas, two major deserts, immense tracts of agricultural land, seven distinct mountain ranges, 1,770 km (1,100 mi) of coastline, and both the highest and lowest points on the continental United States. Further, it is the most ethnically diverse state in the country, with commensurate heterogeneity of life-style. It is similarly heterogeneous with regard to human service resources, exemplified by the physician-to-population ratio, which ranges from nearly twice the national average in parts of the San Francisco Bay Area to one county that does not have a single resident physician. With 61 local health jurisdictions, some large or reporting many AIDS cases and others small or with no reported AIDS cases, each of these jurisdictions has experienced the impact of the HIV epidemic differently. To date, about two thirds of California's AIDS cases have been reported from San Francisco and Los Angeles counties.[4]

Second, knowledge about the pathophysiology, natural history, prevention, and treatment of HIV disease has developed rapidly, especially in the first five years of the epidemic. More has been learned about HIV disease in a shorter time than about virtually any other disease in history. Consequently, the state's approach to the epidemic has had to be flexible enough to accommodate and apply the latest information and scientific developments as they have been discovered.

Third, since first being recognized, HIV disease has affected certain communities and certain groups more than others. Some communities—San Francisco, for instance—have experienced a substantial impact, while others have yet to see their first case. While no community in California will escape the effects of the epidemic in the future, this historically important and continuing disproportionate impact has affected statewide efforts and is a reason why local planning, within the context of overall state guidance, is so important.

Fourth, in addition to its medical and public health considerations, HIV disease entails a number of sociopolitical issues about which there are wide-ranging opinions. Indeed, there has never been a disease in which health considerations have been so intertwined with issues of personal morality and sexuality; social issues of race, class, and family; philosophic concerns about individual and social responsibility; and matters of politics and economics. Again, this complicates statewide planning for the epidemic and underscores the need for local jurisdictions to tailor approaches to the disease to the circumstances of their individual communities.

Fifth, the complexities of HIV disease and the size and diversity of California make it clear that no one approach or strategy will adequately address the needs of HIV disease prevention and treatment programs in this state. Considering the disparate nature of the groups of people who have been infected with the disease and the varying nature of the communities in which these persons live, it is clear that a multifaceted and multidimensional approach to the disease must be undertaken.

Given these difficulties, it is imperative that each local health jurisdiction, using the latest information available, develop its own plan for the prevention and treatment of HIV disease in ways best suited to its citizens.

California's Approach to the HIV Epidemic

To combat the HIV epidemic within the above context, California has developed a five-point approach based on sound medical and public health principles. This strategy has been designed to be flexible enough to accommodate the changing nature of the epidemic and the great diversity of California, as well as to be sensitive to the concerns, fears, and sensibilities of all Californians.

The five-point California approach to the HIV epidemic entails the following components:

- Epidemiologic surveillance;
- Prevention education;
- Provision of medical treatment and supportive services;
- Research; and
- Continuous planning, evaluation, and coordination of programs.

Epidemiologic surveillance has included such activities as establishing an AIDS reporting system (the AIDS Registry) in March 1983, implementing the Alternative Test Site program, ascertaining HIV seropositivity among blood donors, and completing special seroprevalence studies.[5,6] A number of other activities in this regard currently are under way, and additional studies are planned for the future.

Prevention education has been our highest priority in the battle against HIV disease and will remain the focal point of our arsenal because neither a cure nor a vaccine for HIV infection is likely to be developed in the near future. Indeed, 29% of the $77.1 million appropriated to CDHS for AIDS in the past five years has been for prevention education. Overall, from fiscal year 1983-1984 through 1987-1988, California has appropriated a total of $117 million in state funds for the fight against HIV disease.

Specific prevention education activities have included providing funding for nonprofit community-based organizations and local health departments to conduct HIV disease prevention education programs, targeting special educational efforts at alternative test sites, developing various educational instruments for selected groups and the general public, and conducting a statewide AIDS education campaign.[7-10]

Activities undertaken with regard to medical treatment and supportive services include providing care through the Medi-Cal and California Children Services programs, as well as county health service programs[11-13]; initiating nearly 30 home health and attendant care pilot projects; submitting an application for a home and community-based care waiver to the federal Health Care Financing Administration; developing regulations to provide services in hospices[14]; pursuing legislation to establish a new category of licensed health care facility for persons with AIDS; and initiating or collaborating on various HIV disease cost-of-care studies.

The California state government approach to AIDS research has been unique in the nation. It has included the

generous support of research through the University of California and other academic institutions, implementing an HIV vaccine development program, a state-only effort to expeditiously make available new drugs for AIDS treatment, and providing funding for a special HIV disease research institute at San Francisco General Hospital and Medical Center.

Finally, while less tangible than the other elements of the state's HIV disease control strategy, evaluating and coordinating programs are just as important as the other components and are identified separately in our strategy to highlight their importance. To assist in this regard, CDHS has convened various advisory groups and task forces, including a state AIDS leadership committee.

While much has been done at the state level, it is anticipated that additional issues and programs will need to be developed in the future. We think, however, that these need to be developed and implemented within the context of local planning. Such combined state and local efforts are imperative in light of the fact that there is no quick solution to the HIV epidemic—that is, HIV disease prevention and treatment programs must be designed for the long term. These efforts must be flexible and capable of changing quickly as new data emerge. It is also important to note that because HIV transmission involves sexual activity and the use of illegal drugs, it is inevitable that some persons will be offended by certain aspects of HIV disease prevention and treatment programs. Clearly, programs should be designed to offend as few people as possible, but it is not realistic to expect that effective intervention programs for this disease can be implemented and not displease some persons.

In an effort to meet the challenges presented by the HIV epidemic, the CDHS has proposed a framework for local AIDS prevention and treatment program planning, with the goal that local health jurisdictions will develop plans that use most effectively the prevention and treatment resources available in their communities.[1] Such efforts will facilitate state planning, especially by identifying statewide needs and special needs existing within local jurisdictions. The purpose of the proposed framework is to identify those areas in which particular attention should be focused by the local jurisdiction. To do this, we have delineated the fundamental elements that should go into local plans and describe what we think should be the role of state government, realizing that both local and state plans are meant to be living frameworks that, although designed for the long term, will nevertheless evolve over time.

The Role of the California Department of Health Services

Local planning for the prevention and treatment of HIV disease in California should be pursued with an understanding of the role of the California Department of Health Services because CDHS has been designated as the lead agency for AIDS-related matters for California state government. A similar designation to the state health department has been made in most other states.

Although the role of the state health department is in many ways similar to that of a local health department, in other ways it is unique to state government. The various roles of CDHS are briefly summarized in Table 1. While other state health departments share many of these same roles, individual state differences exist; in such cases, this model can be modified accordingly.

TABLE 1.—*Role of the California Department of Health Services in HIV Disease Planning and Program Implementation*

Help establish general state policy
Promulgate overall state goals and program guidelines
Facilitate the efforts of local, state, and federal agencies
Serve as a convening authority
Provide technical assistance, including the review and approval of local plans
Operate and monitor statewide programs
Obtain, dispense, and coordinate state and federal funding
Initiate and conduct or oversee special studies
Collate and disseminate information

HIV = human immunodeficiency virus

The primary responsibility of CDHS, in consultation with the California AIDS Leadership Committee and other relevant groups, is to help establish general state policy and overall state goals and program guidelines for the prevention and treatment of HIV disease. Further, the role of CDHS is to guide, consult with, and support local health jurisdictions to ensure that the most advanced and effective HIV disease prevention and treatment programs are functioning throughout the state. CDHS—and its Office of AIDS in particular—will provide technical and other assistance to local jurisdictions in formulating plans for HIV disease prevention and treatment programs. Insofar as it is possible, CDHS will maintain and make available a team of experts in each program element—epidemiologic surveillance, HIV antibody testing, prevention education, medical treatment and supportive services, and health care financing mechanisms—to assist local jurisdictions in developing plans and implementing programs. Field staff will be available to assist local personnel on a day-to-day basis.

Although there are no current statutory requirements for state review and approval of local HIV disease plans in California, it is thought that the best allocation and the most effective use of state funds can be made by ensuring that each local jurisdiction has an appropriate HIV disease prevention and treatment plan that is consistent with overall state goals and priorities and that state funding be tied to the plan.

CDHS also has responsibility for implementing, operating, and monitoring various statewide programs and activities. Such activities include the California AIDS Reporting System, the Alternative Test Site program, and blood bank surveillance. CDHS also is responsible for securing Medicaid waivers from the federal Health Care Financing Administration; developing and piloting innovative programs; preparing statewide reports for the California legislature and federal agencies; responding to federal requests for California data; applying for federal grants; convening special workshops, conferences, or other such forums; collating and disseminating information to local jurisdictions; initiating, conducting, and overseeing various HIV disease-related studies; and allocating and coordinating state and federal funding for HIV disease programs.

One of the anticipated benefits of coordinated state and local HIV disease planning is the opportunity to provide needed flexibility in funding for local activities. For various reasons, state funding for AIDS programs in California has been accompanied by specific budget-control language in

past years. This has limited both state and local flexibility in using these funds and has required considerable administrative work in managing contracts and similar processes. This budgetary specificity has resulted in delay in transmitting state funds to local groups and has generated an undesirable amount of bureaucratic work.

Ideally, the state and local funding mechanism would involve the least necessary administrative work; provide necessary accountability, both programmatically and fiscally; permit flexibility and local discretion so that maximum effectiveness would accrue from the use of the limited funds; and stipulate the responsibilities and duties expected and required for each level of government. Obviously, state and federal funds should be distributed to local jurisdictions in accordance with established priorities and overall state and national goals. To ensure that these characteristics of the funding mechanism are met, it is important that local plans provide sufficient detail so that needs can be accurately assessed and that program implementation, management, and evaluation procedures can be assessed.

Developing Local Plans

The California Department of Health Services recommends that each local health jurisdiction develop a three-year HIV disease prevention and treatment plan, realizing that the plan will most assuredly require subsequent modification to accommodate changing circumstances and new data.

An integral part of the local HIV disease plan and a requisite first step are assessing present needs and resources, along with projecting how those needs and resources are likely to change over the ensuing three years.

There are five essential components of a local HIV disease prevention and treatment program that need to be addressed by a local plan:

- Central participatory planning,
- Prevention and testing programs,
- Epidemiologic surveillance,
- Providing treatment and supportive services,
- Coordinating financing mechanisms.

These major program elements and goals are considered minimum requirements. Specifying only these elements should not discourage local jurisdictions from going beyond these basic requirements or lead them to believe that these are all that need to be addressed when circumstances indicate the need for a broader approach or a more detailed plan. Likewise, the focus on local plans should not be construed as discouraging regional approaches to HIV disease prevention and treatment. To the contrary, regional planning is strongly encouraged.

Central Participatory Planning

Key to developing any local HIV disease prevention and treatment plan is the establishment of a local advisory body that can assist and guide local program development and implementation. This body should comprise persons with HIV disease-related expertise and other relevant experience in planning and decision making. Membership should be representative of the various groups affected by HIV disease, including persons with HIV infection and providers of services, as well as community-based organizations involved with HIV disease. A coordinator or team leader should be selected to manage the local program and to coordinate the various local government, private, and community-based organizations involved in HIV disease prevention and treatment. A mechanism should be in place that assures this person immediate access to relevant medical and public health advice.

In California, the state level advisory function has evolved through several iterations. At present, this need is being met by the California AIDS Leadership Committee, a group of more than 30 knowledgeable persons from various backgrounds, that reports to the CDHS.

Prevention and Testing Programs

Simply put, HIV disease prevention programs are directed at interrupting the transmission of HIV. HIV antibody testing is a useful element in the prevention program when the testing is combined with personal education or counseling that, when appropriate, leads to behavior modification. Guidelines for HIV antibody testing in California have been promulgated by CDHS,[15] as have guidelines for HIV partner notification programs.[16] Among the activities that should be included here are the following:

- Preventive education programs designed to effect behavior change in persons engaging in activities known to promote the transmission of HIV. These programs likely will include general public education through the media, schools, worksites, and community service organizations; outreach and targeted education for gay and bisexual men, intravenous drug users, prostitutes, homeless persons, and other persons at high risk; special HIV antibody testing and educational programs for local sexually transmitted disease clinics, drug detoxification and methadone treatment programs, family planning clinics, prenatal care clinics, correctional center medical facilities, and partner notification programs; and medical facility-based HIV antibody testing and prevention education programs for hemophiliacs, blood transfusion recipients, perinatal patients, and hospital workers, among others.
- Prevention education and medical treatment programs for presymptomatic evaluation, monitoring, and prophylactic therapy for HIV-infected persons.
- A means of evaluating local changes in high-risk behavior, the incidence of sexually transmitted diseases, HIV seroprevalence changes, and program outcome.
- Screening of donors of blood and blood products, tissues, and organs.
- Perinatal intervention programs, including screening and counseling at prenatal and family planning clinics.

The prevention plan needs to involve local community-based organizations and especially those organizations that have an established record of activity in this regard. These programs need to be coordinated and integrated into the overall local plan.

Epidemiologic Surveillance

Establishing an appropriate local HIV disease policy and plan depends on knowing the extent, pattern, and trend of HIV infection in the local jurisdiction as well as statewide and nationwide. Thus, the local HIV disease prevention and treatment program must include a means of epidemiologic surveillance to determine and monitor the local incidence and prevalence of HIV infection and on which to base current and future caseload and needs projections.

Treatment and Supportive Services

Local HIV disease plans should specifically address the various medical treatment and supportive service resources of the area to assure access to adequate health care for all persons with HIV infection. In this regard, the local plan should consider the expected patient caseload relative to geography, risk group, ethnicity, and other relevant factors. It should also estimate the present and future resources required to provide care for HIV-infected persons, projected shortfalls in resources, and means by which anticipated shortfalls can be addressed.

Ideally, persons with HIV infection should be "case managed" so that the provision of medical treatment and social support services is coordinated within a comprehensive system of health care.

Among the specific treatment resources that should be considered and arranged for are the following:

- Serologic HIV antibody screening—both anonymous and confidential;
- Presymptomatic evaluation, monitoring, and prophylactic therapy for HIV-infected persons;
- Inpatient care for persons with acute HIV-related illness;
- Extended care for symptomatic persons not needing acute inpatient care, including skilled nursing, home health, and residential care;
- Hospice care; and
- Mental health and support services, including situational counseling, acute psychiatric care, and long-term care for HIV dementia.

In addition to the above, the local plan should include mechanisms to address legal issues related to human rights, discrimination, patient privacy, mandated testing, patient isolation, and civil commitment because these are likely to arise. And while civil liberties are not traditionally a focus of health planning, such issues are so intimately associated with HIV disease that a means to address them should be viewed as a key component of any HIV disease prevention and treatment plan.

Coordinating Financing Mechanisms

The financing of HIV disease prevention and treatment services involves a mix of public and private funds, from both local and distant sources. Insofar as public funds may originate from multiple local, state, and federal agencies, it is essential that a mechanism exist for coordinating the various financing mechanisms. Likewise, a means needs to exist whereby funds can be rapidly distributed to local entities while maintaining the requisite programmatic and fiscal accountability.

In the same vein, a means to evaluate the cost-effectiveness of the various HIV disease prevention and treatment components is essential to ensure continued support of these programs.

Conclusion

As health care practitioners, public health professionals, and policymakers, we are challenged to develop effective HIV disease prevention and treatment programs that are comprehensive yet flexible enough to accommodate the resource, caseload, cultural, and sociopolitical diversity of California. We think the model presented here will be helpful in that regard.

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Information

Serum Lactic Dehydrogenase Predicts Mortality in Patients With AIDS and *Pneumocystis* Pneumonia

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Serum lactic dehydrogenase (LDH) activity was compared with mortality in patients with the acquired immunodeficiency syndrome (AIDS) and Pneumocystis carinii *pneumonia during the first four days of admission to assess the test's predictive value. In 30 admissions, 29 patients who survived an episode of* Pneumocystis *pneumonia had a mean LDH value of 385 IU, with five values greater than 520 IU. Eight with pneumonia who died had a mean value of 926 IU; all had values higher than 520 IU. The mean LDH values for 20 patients with AIDS (35 admissions) who survived and 4 who died of non-*Pneumocystis *disease were 240 IU and 350 IU, respectively; these patients were the control population. The positive and negative predictive values for survival using 520 IU as the threshold are 61% and 100%. Thus, LDH measurements in the first days of admission for* P carinii *pneumonia predict mortality and are useful in guiding future management.*

(Lipman ML, Goldstein E: Serum lactic dehydrogenase predicts mortality in patients with AIDS and *Pneumocystis* pneumonia. West J Med 1988 Oct; 149:486-487)

Pneumocystis carinii pneumonia, one of the commonest life-threatening opportunistic infections in patients with the acquired immunodeficiency syndrome (AIDS), has an unpredictable clinical course.[1,2] Because predicting the clinical outcome of a *Pneumocystis* infection is important in counseling patients and families, in determining the potential benefit of intensive therapy with invasive pulmonary procedures, and in comparing institutional results, we compared serum lactic dehydrogenase (LDH) levels in patients with AIDS and *Pneumocystis* infections and those without *Pneumocystis* infection to assess this test's predictive value. LDH was selected because elevations in LDH correlate with the extent of *Pneumocystis* infection in patients with AIDS.[3]

Patients and Methods

The medical records of all adult patients with AIDS admitted to the University of California, Davis, Medical Center (UCDMC) between January 1, 1984, and November 1, 1987, were reviewed for the diagnosis of *P carinii* pneumonia. AIDS was diagnosed in accordance with the criteria of the Centers for Disease Control.[4] *P carinii* pneumonia was diagnosed by finding *P carinii* organisms in pulmonary lavage or biopsy specimens. LDH levels were determined enzymatically on a Technican RA-1000 (Technican Instruments Corporations, Tarrytown, NY), with normal values being 110 to 200 IU in our laboratory. When more than one LDH value was determined in the first four days of admission, the highest value was compared with the clinical outcome. Arterial blood gas values with the patient breathing room air were available in 17 patients (13 survivors, 4 deaths).

Results

A total of 51 adult patients, aged 24 to 69, had 90 AIDS-related admissions to UCDMC from January 1984 to November 1987. *P carinii* pneumonia was documented in 37 admissions (33 patients), and in all but one case, the chest x-ray film showed an interstitial infiltrate. The one x-ray film without an interstitial infiltrate showed diffuse pulmonary nodules. The alveolar oxygen tension (PAo_2) values ranged from 52 to 77 torr, with the lower values of 52 to 68 torr being present in both groups (four survivors, three nonsurvivors). The PAo_2 values for the two groups could not be compared because of the nonuniform fraction of inspired oxygen that patients received. All were treated with trimethoprim-sulfamethoxazole. Eleven patients—seven survivors and four nonsurvivors—also received pentamidine.

Figure 1 shows the relationship between the LDH value and the clinical course for patients with *P carinii* pneumonia. The mean LDH value for the 29 patients (30 admissions) who survived was 385 IU with a range of 202 to 866 IU. Two of the five LDH values above 520 IU were in patients with hepatobiliary disease; the other three did not have a nonpulmonary cause for their high LDH values. These three patients received intravenous corticosteroids in addition to their anti-*Pneumocystis* therapy. The mean LDH value in the eight patients with *P carinii* pneumonia who did not survive was 926 IU with a range of 521 to 1,413 IU. This result was typically obtained on the third or fourth hospital day and in a few cases represented an increase from the value reported on admission. The mean LDH value in the 35 admissions for non-*Pneumocystis* disease in which the patient survived was 240 IU and the range varied from 126 to 521 IU. The speci-

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This study was supported by a grant from the University of California Task Force on AIDS.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
LDH = lactic dehydrogenase
PAO_2 = alveolar oxygen tension
UCDMC = University of California, Davis, Medical Center

mens for 20 of these values were obtained on the third or fourth hospital day. The LDH value of 521 IU was in a patient with hepatobiliary disease. Four patients without *P carinii* pneumonia died, and in this group the LDH values varied from 200 to 480 IU. This group included one patient with pulmonary *Mycobacterium avium-intracellulare* and one with overwhelming pneumonia due to *Staphylococcus aureus, Haemophilus influenzae,* and cytomegalovirus infection. The increased occurrence of abnormally high LDH values in each group reflects the high incidence of hepatic abnormalities in patients with AIDS.

Positive and negative predictive values calculated from the above data using an LDH value of 520 IU as the threshold were 61% and 100%, respectively.

Comment

This study shows that the highest serum LDH determination within the first four days of admission can be used to predict the course of *Pneumocystis* pneumonia in patients with AIDS. Values of less than 521 IU predict a favorable therapeutic outcome. In contrast, values above 521 IU predict an unfavorable outcome unless another cause in addition to that of *Pneumocystis* can be found for the elevation.

The above conclusions are consistent with previous reports indicating that the LDH levels are uniformly elevated in patients with *Pneumocystis* pneumonia and that mean peak LDH levels tend to be lower in survivors.[3,5] The present studies extend these observations by showing a threshold level below which death is unlikely to occur.

The elevations in serum LDH activity can be attributed to uncontrolled B-cell proliferation[6,7] and destruction of lung tissue.[8] If this is the case, it is reasonable to expect that corticosteroids may suppress the immune response to *Pneumocystis,* the resultant lung destruction, or both. There have been at least two reports of the efficacy of using corticosteroids in patients with *P carinii* pneumonia.[9,10] This is notable because, of the five surviving patients with *P carinii* pneumonia in our study with significantly elevated LDH values, three received adjuvant corticosteroids. Silverman and Rubenstein documented an association between uncontrolled B-cell proliferation and elevated serum LDH levels in patients with AIDS who had interstitial pneumonitis.[3] These investigators showed that such patients have elevated serum immunoglobulins, high baseline in vitro lymphocyte proliferation, and extensive lymphoplasmacytic infiltrates in the lungs and lymph nodes.[3]

Destruction of lung tissue also contributes to elevations in serum LDH levels. Such elevations occur in 80% to 90% of patients with pulmonary infarctions due presumably to the destruction of pulmonary tissue.[8] Because *P carinii* infections cause lung tissue destruction in patients with AIDS,[11] this pathologic process would also result in elevated enzyme levels. Thus, patients with AIDS who have more severe *Pneumocystis* infections and are therefore likely to die would be expected to have higher serum LDH activities due to more uncontrolled cell proliferation and greater tissue destruction. LDH isoenzyme fractionation may increase the specificity of LDH levels and should be evaluated.

Our observations showing a threshold level of LDH activity with a 100% negative and 75% positive predictive value for the outcome of a *Pneumocystis* infection in patients with AIDS has potential clinical usefulness. This objective marker can be used to identify patients with good prognoses. The marker is also useful for assessing therapeutic benefits. For example, in the five surviving patients with *P carinii* pneumonia in our study who had levels of LDH activity above 521 IU, three received steroids in addition to antimicrobial therapy, suggesting that the marker is useful in confirming a favorable therapeutic result. Last, the marker can be used to compare the severity of disease for cases reported from different institutions.

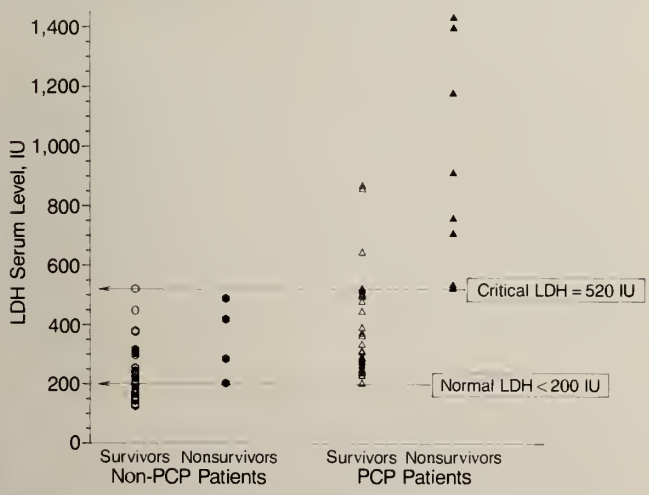

Figure 1.—The graph shows the relationship of serum lactic dehydrogenase (LDH) activity to survival in patients with AIDS who did and those who did not have *Pneumocystis carinii* pneumonia (PCP).

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Lessons From the Practice

On Not Growing Accustomed to Death

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"Each death takes you back to the ones before," I was taught in my hospice training. I was a second-year medical student at the time and had experienced death, that of my grandparents, only in a distant way, a way that made much of the hospice training abstract.

Now a second-year resident, I have seen death many times, in many different contexts. In some respects I have grown accustomed to presiding over death: checking the pulse that I know is not there, breaking the news to the family, trying to comfort them. Frequently I do not know the patient or the patient's family well. I am the cross-cover resident bearing witness to the event, the unsuccessful resuscitator of a patient rushed to the emergency department, or the last caretaker of a patient brought to the hospital to die. For me, the hardest part of these deaths is my unfamiliarity with the patient's family. As I step into the waiting room, they lift their expectant faces, and I feel sad, both for the news I bring and for the fact that it is I, rather than a physician they have known in better times, who brings them such sadness. I cannot share in their grief as someone who knew them well would, and so, as I reach for words of comfort, I feel awkward and false.

I have grown accustomed to this awkwardness but not to the pain of losing a patient I have known well. The pain, I recognize, is unavoidable because it's inherent in the work. "The one thing we have to give to the dying is ourselves," a psychiatrist caring for terminal patients taught me. He believed that only by becoming so involved with a patient that their death would hurt you could you genuinely bond with them. The bond is forged from the fear of loss and loneliness that death poses. The added burden that my hospice teacher implied but I did not yet appreciate was that death's toll is cumulative. Each death forces you to relive the ones before, and the pain grows.

Recently a hemophiliac I cared for died of AIDS. There was nothing unexpected about his death. It was as close to the way he wanted to go as circumstances allowed. He was at home with his family, receiving intravenous morphine; the passing was quick and painless. But in my gut it still hurts. There are things I could have done to care for him better, things I wish I would have told him before he was comatose. But I think the reason it hurts is that I miss him. He was a bright and sardonic man who once told me when I was trying to help him make the most out of his rapidly narrowing life, "My greatest asset is my commode; it's the only thing I can use."

His death also pains me because it evokes feelings about the ones that preceded it. A woman awaiting a liver transplant that she and I knew she could never survive kept telling me she had every confidence in me and, when she was well, we would all go out for dinner. "And dancing," I added. A man dying of lymphoma, with his lover and his children at his side in a hospital room full of stuffed animals, told me when I asked him how he was, "Better, now that you're here." A man I cared for at home dying of the dementia and wasting of AIDS spent his last days filling out, in his no longer decipherable handwriting, every sweepstakes entry he could find because "I want my lover to have something when I'm gone."

After each of these deaths I cried—for all of them, for all I could have done better, for not wanting them to die (even the ones I took on as hospice patients), and for myself, who misses them. And with each new patient with a life-threatening illness, there is a moment of reticence when I wonder if another loss would be overwhelming.

A patient comes into my office for a follow-up visit. On physical examination I see a sign I have watched for and feared: a Kaposi's sarcoma lesion. He will need a biopsy to be sure, but the appearance of the lesion is classic. "How long has it been there?" I ask. "Three weeks. I hoped it would go away." "Do you know what I'm worried about?" He nods his head. He, too, has seen Kaposi's sarcoma lesions; he, too, has lost friends to the illness. I explain the biopsy procedure to him. "How soon can we get it done with?" he asks. The fear and sadness in his eyes are replaced by a look of pure courage. I take my cue from him: I put my arm around his shoulder and walk him to the door.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors. Articles should be 800 to 900 words.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
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(Katz MH: On not growing accustomed to death. West J Med 1988 Oct; 149:488)

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Commentary

Trust at Risk

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Fortunately, most people still seem to think highly of their own physicians, even though they may have considerable doubt about physicians in general. They tend to trust their own physician, even if he or she is no more expert than the rest. *Un*fortunately, the presence or absence of trust is something that is never addressed in discussions of health economics and health policy. Without trust, however, it is frightening to be a patient and difficult to be a physician. In order to trust, a patient must believe the physician has at least average competence and will place the patient's welfare uppermost among competing considerations. Despite some exceptions, this has been the usual situation. But how sure are we that it will be so in the future?

The nature of medical practice is changing. More than 500 HMOs and a similar number of PPOs—plus an assortment of other types of discount health plans—have emerged to compete with traditional fee-for-service practice. Aimed at limiting rising health costs, the three-letter plans are dividing physicians into two groups that are being cast in adversarial roles.

First there are the primary physicians, typically internists, pediatricians, and family and general practitioners. Physicians in these groups are generally the first to be called for most health problems. They are the ones most likely to know patients personally and to maintain long-term relationships with them. As "family doctors," they can ordinarily expect the development of bonds of trust between themselves and their patients.

Other physicians, classed as consultants, constitute many specialties and subspecialties ranging from dermatology to cardiac surgery. It is an article of faith in cost-sensitive health plans that some kind of roadblock must be placed between consultants and patients—something that traditional health insurance did not do. Now, for example, when a patient wants to see a subspecialist, it may require the permission of a primary physician in order to obtain insurance coverage.

This is beginning to create a two-class system within medicine. Primary physicians are increasingly obliged to act as "gatekeepers" on behalf of health plans that compete with one another mainly on the basis of price. By keeping expensive referrals to a minimum, they improve the balance-sheet of the plan but deprive their colleagues of work and income. Other physicians must wait in the wings until they are summoned.

Why would primary physicians want to take on the disagreeable task of standing between patients and all other physicians? The answer is that few do. In fact, a number of widely heralded plans such as SAFECO's in Seattle failed because primary physicians were not sufficiently stringent in limiting referrals. The same pattern has occurred with plans caring for Medicaid patients, causing one demonstration project in Monterey, California, to also founder in the red ink of specialty consultations.

This has led to the practice of giving primary physicians an "incentive" to approve referrals only sparingly. Typically a certain percentage of fees is withheld pending an audit of the plan's experience. If the year has been profitable, the money is turned over to the physicians. If not, the plan, rather than the physicians, gets the money. (Though consultants may also have part of their fees held back, they are not involved in gatekeeping.) The term used to describe this process is putting the physician "at risk."

This concept is now being pushed further. San Mateo County, California, is experimenting with a new Medicaid plan. In it, primary physicians are "capitated"—that is, they are given a set sum per patient each month to provide whatever care is needed. The pay is modest and in many instances is not enough to cover the cost of providing that care.

There is a gimmick, however. It involves using the separate pool of money that has been set aside for normal use by specialists and hospitals as a lure for the primary physicians. Should they keep referrals down to the point where money is left over at the end of the year, they get a share of the pot that would otherwise have gone to their colleagues or to the hospitals.

Thus, primary physicians are rewarded for not providing care, whereas other physicians are paid for what they do to help patients. This basic difference goes far beyond any question of disparity in earnings or of whether "thinking" or "doing" is compensated appropriately. Will the public continue to trust physicians and will physicians be able to trust one another in such circumstances?

Capitated plans are appearing commonly in the private sector. These, too, place the brunt of the economic risk selectively on primary care. There is a certain irony in this because the earnings of the primary care specialties are already the lowest in medicine. The status and prestige of primary physicians are beginning to erode accordingly. This is neither a happy nor a healthy development.

In bygone days, the competence and character of physicians inspired admiration and trust. Now we must be concerned with the intrusion of extraneous factors that are manipulative and that distort normal medical motivation. The current climate, with its emphasis on contracts and markets, and with little or no honor offered for character and, at times, even competence, is potentially divisive and dangerous.

It is doubtful that anyone in or out of medicine is particu-

(Alper PR: Trust at risk. West J Med 1988 Oct; 149:489-490)

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larly pleased with the prospect of primary physicians having to weigh their own economic well-being directly against their patients' needs. But the primary care dilemma is that by not "squeezing the primaries," to use the jargon of the insurance industry, it is difficult (if not impossible) to restrain overall spending. A credible way out of this dilemma will do much to preserve the compact of trust between American physicians and their patients.

Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

The Consequences of Chromosome Imbalance—Principles, Mechanisms and Models

Charles J. Epstein, MD, Professor of Pediatrics and Biochemistry, University of California, San Francisco. Cambridge University Press, 32 E 57th St, New York, NY 10022, 1986. 475 pages, $59.50.

Charles Epstein has written a scholarly book about the chromosomes. The clinician who needs a catalog to help him or her put together the various pieces of a syndrome represented by a patient in a way that suggests a specific cytogenetic diagnosis or at least leads him or her to order a karyotype will find today many catalogues of cytogenetic diseases. This book is different. It represents a concerted attempt to understand, as thoroughly as data available today will permit, the ways in which chromosomal imbalance produces very highly specific phenotypes of abnormalities.

The organization of the book is interesting. The initial consideration is of the diversity of clinical phenotypic expression of autosomal aneuploidy, with an emphasis on what in the way of general principle can be gleaned from this analysis of clinical experience. The book proceeds to a theoretical approach to the mechanisms by which aneuploidy produces its phenotypic effects and to experimental data bearing on this issue. The author then discusses in detail three prototypes of aneuploidy: trisomy 21, XO monosomy, and chromosomes and cancer.

It is becoming increasingly possible to map just which portions of a chromosome are responsible in aneuploidy for the phenotypic features that identify a syndrome. Thus, the nuclear projections on polymorphonuclear leukocytes that are characteristic of trisomy 13 result from duplication of the very proximal part of the long arm of the chromosome, whereas the typical polydactyly is the result of extra material from the most distal portion. The situation in Down's syndrome is more closely delimited. The full phenotype is present when there is duplication of the area of chromosome 21 delimited by band 21q22. This is the area that contains the genes for the enzyme superoxide dismutase (SOD1), an enzyme that is thought to protect cells from oxygen-containing free radials and phosphoribosylglycinamide synthetase (PRGS), an enzyme of purine synthesis. Superoxide dismutase is the prototypical enzyme in which careful studies of enzyme activity indicated a gene dosage effect in trisomy 21. The activity in trisomic cells approximates 1.5 times that of normal diploid cells, and the SOD1 messenger RNA is increased to a similar degree. The same increase in enzyme activity in trisomic cells is true of PRGS and other enzymes that have been mapped to this area. Similarly, activity in monosomic cells has been found to approximate 0.5.

Despite these and other specific correlates of the state of trisomy for chromosome 21, it remains difficult to make the jump from any of the known associations to an acceptable pathogenetic mechanism for any of the striking phenotypic features such as mental retardation, immunodeficiency, or the propensity for malignancy. In each case the author has reviewed the extensive literature and its implications in detail and, with appropriate reservation, concluded that we have much more to learn before we can really understand the nature of the relationships.

A feature that has generated considerable recent speculation is the relationship of Down's syndrome to Alzheimer's disease. The brains of adults over 35 with Down's syndrome have histologic changes and neurofibrillary tangles that are indistinguishable from those of patients with Alzheimer's disease. A major component of these plaques is an amyloid beta-protein that is identical in both groups of patients. It may be a lead that since the review for this book was concluded in 1984 the gene for this beta-protein has been mapped to chromosome 21, and it is thought that familial Alzheimer's disease can also be traced to chromosome 21. Similarly, the recent mapping of an oncogene, the *ets*-2 gene, to the 21q22 region may provide the link to the pathogenesis of leukemia and other neoplastic diseases in patients with trisomy 21.

Some of the critical connections may be discovered now that an animal model has become available. This area, first explored by Gropp of Lübeck, has largely been developed by the author and his colleagues. Chromosome 16 in the mouse is homologous with human chromosome 21 with regard to the various loci that have been mapped, including SOD1, PRGS, and *ets*-2. Mice trisomic for chromosome 16 have a phenotype with many of the features of Down's syndrome, including an endocardial cushion defect. Better models may be mice that are trisomic for smaller parts of chromosome 16, and work is under way to produce such animals. Transgenic mice, products of modern recombinant DNA technology, in which single genes or groups of genes are transferred early in development, should permit the very fine dissection of interrelationships between phenotype and genotype.

The author is professor of pediatrics and biochemistry at the University of California, San Francisco. His book will be of greatest use to investigators working in the field. It will also be of interest to clinical geneticists, cytogeneticists, dysmorphologists, and others concerned with the understanding of chromosomal abnormalities. The powerful tools at hand for further investigation of this field promise that it is poised for a major series of advances. We shall look forward with interest to the next edition.

WILLIAM L. NYHAN, MD, PhD
Professor of Pediatrics
University of California, San Diego, School of Medicine
La Jolla, California

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Trandate Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

For references and a complete listing of reported adverse reactions, including incidence at various dosage levels, please see ADVERSE REACTIONS section of the Brief Summary of Prescribing Information on next page.

Please see next page for references and Brief Summary of Prescribing Information.

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References: 1. Malini PL, Strocchi E, Negroni S, et al: Renal haemodynamics after chronic treatment with labetalol and propranolol. *Br J Clin Pharmacol* 1982;13(suppl 1):123S-126S. **2.** Pedersen EB, Larsen JS: Effect of propranolol and labetalol on renal haemodynamics at rest and during exercise in essential hypertension. *Postgrad Med J* 1980;56(suppl 2):27-32. **3.** Wallin JD: Antihypertensives and their impact on renal function. *Am J Med* 1983;75:103-108. **4.** Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. *Br Heart J* 1979;41(2):192-198. **5.** Feit A, Holtzman R, Cohen M, et al: Effect of labetalol on exercise tolerance and double product in mild to moderate essential hypertension. *Am J Med* 1985;78:937-941. **6.** Lund-Johansen P: Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983;75:24-31. **7.** Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:285-293.

TRANDATE® Tablets **BRIEF SUMMARY**
(labetalol hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy before major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see PRECAUTIONS: Drug Interactions).

PRECAUTIONS: General: *Impaired Hepatic Function:* TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will

TRANDATE® (labetalol hydrochloride) Tablets

be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, headache. ***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, taste distortion. ***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, drowsiness. ***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, increased sweating. ***Cardiovascular:*** Edema, postural hypotension. ***Respiratory:*** Dyspnea. ***Skin:*** Rash. ***Special Senses:*** Vision abnormality, vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including, rarely, syncope. ***Central and Peripheral Nervous Systems:*** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment. ***Collagen Disorders:*** Systemic lupus erythematosus; positive antinuclear factor (ANF). ***Eyes:*** Dry eyes. ***Immunological System:*** Antimitochondrial antibodies. ***Liver and Biliary System:*** Cholestasis with or without jaundice. ***Musculoskeletal System:*** Muscle cramps, toxic myopathy. ***Respiratory System:*** Bronchospasm. ***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia. ***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents. ***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on psychometrics. ***Cardiovascular:*** Intensification of AV block (see CONTRAINDICATIONS). ***Allergic:*** Fever combined with aching and sore throat; laryngospasm, respiratory distress. ***Hematologic:*** Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. ***Gastrointestinal:*** Mesenteric artery thrombosis, ischemic colitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

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(Continued on Page 496)

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(Continued from Page 495)

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Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

FAMILY PRACTICE, CASHMERE, WASHINGTON. Family Practitioner for two MD office. Vacancy opening July 1989. Cashmere is on the eastern edge of the Cascades 10 miles west of Wenatchee, our 167-bed hospital location. It's a scenic spot in a fruit-growing valley. Schools are highly rated and recreation is tops. Call duty will be shared with two MDs in a separate office. Please contact Edgar A. Meyer, MD, 303 Cottage Ave, Cashmere, WA 98815; (509) 782-1541 or 782-2571.

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available in all specialties with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; 1 (800) 544-1987.

PACIFIC NORTHWEST

The Wenatchee Valley Clinic, a multispecialty group of 105 physicians, has several practice opportunities throughout its seven practice locations. Currently we are seeking:

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- Dermatology
- OB/GYN

All positions offer an excellent compensation and benefit package. North central Washington provides a high quality of life for those interested in an abundance of recreational opportunities in a family-oriented rural setting. If interested, send your CV to Dr Gerald Gibbons, Medical Director, Wenatchee Valley Clinic, 820 N. Chelan Ave, Wenatchee, WA 98801, or call (509) 663-8711, ext 205.

SACRAMENTO, CALIFORNIA. Family Practitioners and Internists needed part-time for staffing ambulatory care clinic. Our clinic operates seven days a week during days and evenings and provides episodic care on a same-day basis. Physicians may choose to work one to 10 half-days or evenings per week with wide flexibility. Full benefits and retirement if working six or more half-days a week on a steady basis. Please call John Petitt, MD, (916) 973-5560 or send CV to John Petitt, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825.

GENERAL INTERNISTS. BC/BE General Internists needed for multispecialty group. We are experiencing robust growth and are seeking Internists to join large established Department of Medicine with University affiliation. Our hospital provides integral part of University of California, Davis housestaff training program. Pleasant outpatient practice setting is in six to nine physician modules. Excellent starting salary with rapid early advancement and steady yearly salary growth thereafter. Full benefits and retirement. This is an outstanding practice opportunity. Please call Dennis Ostrem, MD, Chief of Medicine, The Permanente Medical Group, Inc, (916) 973-5781 or send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825.

(Continued on Page 498)

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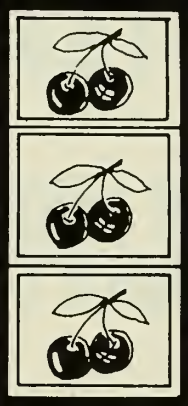

CLASSIFIED INFO (415) 882-5178

(Continued from Page 496)

PHYSICIANS WANTED

LOCUM WANTED. Pediatrician, BC/BE, competent, reliable, with Utah license, for three to six weeks Nov/Dec/Jan, April, Aug/Sep. $1,100 per week, malpractice, accommodations provided. PO Box 1915, Cedar City, UT 84720; (801) 586-0300.

HEMATOLOGIST-ONCOLOGIST. Northern California Permanente Medical Group seeking a second Oncologist with Hematology BC/BE for a new medical center facility. Progressive group offers excellent financial package and benefits in the setting of the northern California wine country. Young university hospital trained medical department in a quality professional, social, and recreational environment. Academic affiliation and resident teaching available and encouraged. Reply with CV to Nicholas O. Iannotti, MD, 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

FAMILY PRACTICE PHYSICIAN (BC/BE) to join four-site four physician practice at community/migrant health center in large agricultural valley surrounded by mountains in southern New Mexico bordering Texas and Mexico. City (65,000 population) has state university and military contract industry; good job opportunities for spouse. Full Family Practice with limited OB and in-patient care at local 268-bed hospital. Center serves as teaching site for various health and medical students. Center is a loan repayment program which may defray $20,000 per year. Competitive salary with good benefits which include pension, malpractice, health insurance, CME, and others. Send CV to Mary E. Bane, Project Director, La Clinica de Familia, PO Drawer D, San Miguel, NM 88058; (505) 233-4270. Start date July/August 1989.

PHYSICIANS WANTED

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Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

GENERAL INTERNIST OR INFECTIOUS DISEASE SPECIALIST. General Internist or Infectious Disease Specialist wanted to join busy four person Internal Medicine group in San Diego, California. Position available immediately. Guaranteed income or percentage of collection, whichever is greater, with an opportunity for full partnership in two years. Earning potential the first year is 100 K plus, and second year 150 K plus. Reply to Number 119, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN. San Francisco bay area prepaid medical group with new LDR suite and family centered Obstetrical practice as well as full Gynecological practice has opening with competitive salary and generous benefit package. Send CV to Mary Ann Miner, MD, Chief, OB/GYN Department, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063.

IMMEDIATE OPPORTUNITY for full- or part-time work in general Internal Medicine and/or Urgent Care. Large HMO practice in Marin County. Contact Jonathan Freudman, MD, Assistant Chief, Department of Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903; (415) 499-2357. An Equal Opportunity Employer.

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RHEUMATOLOGIST. Excellent opportunity to join successful HMO practice in desirable Marin County. Contact Jonathan Freudman, MD, Assistant Chief, Department of Internal Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903; (415) 499-2357. An Equal Opportunity Employer.

INTERNIST WANTED. Dynamic, expanding Beverly Hills area group seeks two Internists capable of giving high quality, compassionate care to good mix of fee-for-service/managed-care patients. Congenial group offers competitive salary, medical/dental/malpractice/disability package, profit-sharing, and partnership potential. Respond with CV to Medical Group of Beverly Hills, 5901 W. Olympic Blvd, Ste 201, Los Angeles, CA 90036, Attn: Medical Director.

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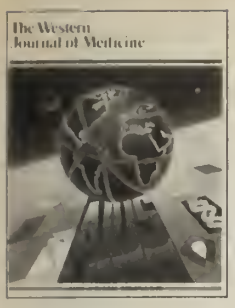

AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director,
Special Programme on AIDS
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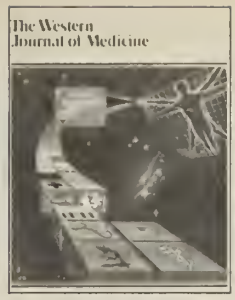

Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

—Marsden S. Blois, PhD, MD

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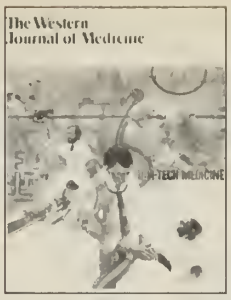

High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

—R. Paul Robertson, MD

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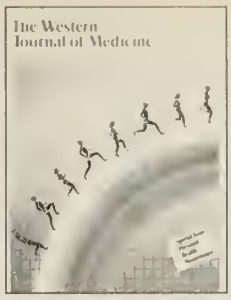

Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

—John H. Holbrook, MD

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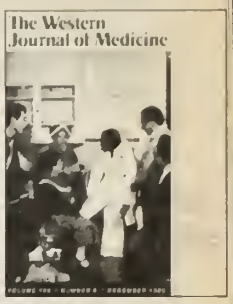

Cross-cultural Medicine

Reprinted as a book because of extraordinary demand

The barriers may be great indeed when an American-trained physician undertakes to treat a patient from another ethnic or religious background. Too little attention has been given to developing better or even adequate communication across all these different cultures. The subject is of worldwide social, economic and political importance, and on a more individual and personal basis it is important in patient care.

—Malcolm S.M. Watts, MD

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OCCUPATIONAL MEDICINE. Eisenhower Immediate Care Centers has an immediate opening for Medical Director, Occupational Medicine, combining actual clinical practice with medical management. The Centers are affiliated with Eisenhower Medical Center, located near Palm Springs, California; only two hours drive from Los Angeles and San Diego. California license, previous Occupational Medicine experience or Occupational Medicine certificate, competitive salary guarantee, malpractice paid. Send CV to Jim Manion, MD, 67-780 E. Palm Canyon Dr, Cathedral City, CA 92234; (619) 328-1000.

EMERGENCY MEDICINE. San Francisco. Full-time position in active emergency department with housestaff training program and excellent subspecialty back-up. Competitive salary, outstanding benefits. For information call Steve Lauterbach, MD, Assistant Chief, Emergency Department, Kaiser San Francisco, (415) 929-4020.

SURGICAL ONCOLOGIST. A position is available for a well trained Surgical Oncologist to join an established multidiscipline group in Long Beach, California. Please send CV to PO Box 30, Long Beach, CA 90801.

FAMILY PRACTICE/URGENT CARE PHYSICIAN, BC/BE to staff Immediate Care Center of 35 physician multispecialty clinic in southeastern Washington. Excellent compensation and benefit package. Send CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

PHYSICIANS WANTED IN TEXAS AND OKLAHOMA. Major cities to rural communities. Cardiology, ENT, Family Practice, General Surgery, Internal Medicine, OB/GYN, Oncology, Orthopedic Surgery, Pediatrics, Psychiatry, Radiology. Excellent quality of life, first year guarantee, etc. Reply with CV or call Armando L. Frezza, Medical Support Services, 8806 Balcones Club Dr, Austin, TX 78750; office: (512) 331-4164, 24 hour FAX (512) 331-6741.

INTERNIST. Yucca Valley, California. Expanding practice needs associate. CV to Delta Hi-Desert Medical Group, 915 Camino Del Mar, Ste 100, Del Mar, CA 92014.

SACRAMENTO. BC/BE Family Physicians needed for full-time primary care clinic, part-time ER/part-time primary care clinic, or full-time in our ER. We are a large-staff model HMO offering competitive salary, excellent benefit package, and shareholder status. California license required. Contact Richard Fury, MD, 1001 Riverside Ave, Roseville, CA 95678 or call (916) 784-4620. EOE.

DIRECTOR OF DIVISION OF NEUROSURGERY. Progressive BC/BE Neurosurgeon to reorganize the Division of Neurosurgery at a major trauma and teaching center. Should be eligible for academic appointment at a major medical school. Compensation is a combination of teaching and administrative pay plus fee-for-service. Contact Francis L. Comunale, MD, Medical Director, San Bernardino County Medical Center, 780 E. Gilbert St, San Bernardino, CA 92404.

INTERNIST. Needed to establish a group practice in Redding, California. Excellent opportunity leading to a partnership. First year salary guaranteed. Must be BE/BC in Internal Medicine. Use all of your hospital and consultative skills in an area not overcrowded by subspecialists. Progressive hospital with open heart program and active ICU/CCU. Send CV to 2240 Court St, #B, Redding, CA 96001.

OREGON COAST. Busy fee-for-service multispecialty group looking for additional Internist and Family Practitioner including OB to work with two Internists and three Family Practice Physicians. Well-equipped clinic next to 34-bed hospital with eight ICU/CCU beds and two new birthing rooms. Top-notch school system and just 75 miles to Portland. Send CV or call Rick Bigger at North Coast Medical Center, PC, 727 Wahanna Rd, Seaside, OR 97138; (503) 738-9551.

CALIFORNIA—CENTRAL COAST. Due to continued growth in our group we have immediate need for OB/GYN, Internal Medicine, Family Practice Physician, and Pediatrician. Income commensurate with background/experience. Send résumé to Arbor Medical Group, Attn: R. Bunch, 1414 E. Main St, Santa Maria, CA 93454, or call (805) 922-5027.

ANESTHESIOLOGIST, BC/BE. Position immediately available to join four Anesthesiologists. Beautiful coastal community in southern California. No open-hearts. Competitive salary plus malpractice insurance. Send CV to Department of Anesthesia, Ventura County Medical Center, 3291 Loma Vista Rd, Ventura, CA 93003; (805) 652-6239.

INTERNIST, BC/BE, California license. Group practice opportunity. Outpatient and hospital practice. Guaranteed income. Send résumé to Dr Susann J. Steinberg, Access Health Care, 26 California St, San Francisco, CA 94111.

PSYCHIATRIST. The University of Wyoming is now seeking a Psychiatrist for academic year appointment. Candidate must be a graduate of an approved medical school, have completed an approved residency program and be BC in Psychiatry. Selected candidate must have demonstrated the ability to work with college age students. Candidate must also demonstrate knowledge and ability to develop innovative mental health care clinics and supervise other mental health providers as well as postgraduate students. Candidate must be licensed to practice in Wyoming or qualify for licensure. Selected candidate will join five health care providers to care for 10,000 students in Laramie, Wyoming. Salary commensurate with qualifications and experience. Opportunity exists for part-time practice or affiliation with expanding Mental Health facilities in the Laramie area. Closing date is November 16, 1988. The University of Wyoming is an Equal Opportunity/Affirmative Action Employer. Send CV to Thomas E. Cronkleton, MD, Acting Director, Student Health Service, University Station Box 3068, Laramie, WY 82071.

CARDIOLOGIST NORTHERN ARIZONA

A busy, well-established invasive Cardiologist in Cottonwood, Arizona is seeking an invasive or non-invasive Cardiologist to join him. He is the only Cardiologist in a service area of 15,000 and refers his caths and surgical patients to the Arizona Heart Institute in Phoenix. Cottonwood is located 35 miles south of Flagstaff, 18 miles west of Sedona, and 85 miles north of Phoenix.

For further information about this private practice opportunity, send your CV to: Manager, Professional Relations, Humana Inc., Dept. HH-9, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

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INTERNAL MEDICINE. San Francisco bay area—immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical housestaff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119.

RHEUMATOLOGIST. Immediate opening for BC/BE Rheumatologist with large prepaid group practice in San Francisco bay area. Busy clinical practice with opportunities for teaching and research. University appointment possible. Competitive salary. Generous benefit package. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, Permanente Medical Group, 260 International Cir, San Jose, CA 95119 or phone (408) 972-6560.

GENERAL PRACTICE. Busy medical center needs full-time physicians for urgent appointments. Significant evening and weekend hours. Abundant free time with no on-call responsibility. Excellent benefits and retirement program. Kaiser Permanente, Santa Teresa Hospital, 250 Hospital Parkway, San Jose, CA 95119; (408) 972-6180.

FAMILY PRACTICE. Outstanding opportunity for a Family Practice couple or two Family Practice Physicians to purchase a well established practice in northern California near Sacramento. The practice includes equipment, nicely appointed office, large patient volume, and excellent staff. Negotiable terms. Please call collect Physician Relations Manager, (916) 537-5009.

PUGET SOUND. Critical Care Internist to join four-man group. Beautiful waterfront city near Seattle. Infectious Disease experience preferred. Outstanding financial package. Send CV to Number 116, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 502)

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AIR FORCE

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DERMATOLOGIST OPPORTUNITY. Two openings in Phoenix for BC/BE Dermatologists. Six figures to start, paid vacation, malpractice insurance. Join an established, growing practice in an area perfect for family growth and recreation. Reply to: Dee Faber, Administrator, 844 S. Edward, Suite 6, Tempe, AZ 85281; (602) 966-2872.

EMERGENCY MEDICINE, SANTA ROSA. Large HMO seeking one or more ABEM certified or eligible full-time physicians to staff emergency department in hospital presently under construction. Positions available to start January 1989, with practice primarily in San Rafael until the Santa Rosa facility opens in late 1989. Salaried position with wide range of benefits. Send inquiries to Dr John David, Chief, Department of Emergency Medicine, Kaiser Permanente, 99 Montecillo Rd, San Rafael, CA 94903; (415) 499-2400.

PALO ALTO, CALIFORNIA. Family Physician BC/BE to join nine-member department in large multispecialty group. Highly desirable location; excellent benefits. Clinical faculty appointment at Stanford available. Contact Susan D. Smith, MD, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

INTERNIST, with or without subspecialty, to associate with Nephrologist in coastal North Carolina. Riverfront community near beaches. 200-bed hospital with most surgical specialties. Send CV and cover letter to Number 120, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE/GENERAL PRACTICE wanted for full-time practice to work three days a week and share with another Practitioner. Rural setting, good pay, nice people. Can commute for two nights a week, one hour Sacramento, one hour and 15 minutes Nevada City, two hours San Francisco. Contact Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

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NEW MEXICO communities have excellent private practice opportunities available for the following specialties: BC/BE Family Practitioners, Internists, OB/GYNs, and Orthopaedic Surgeons. Financial assistance available on all opportunities. For further information, please submit CV to Bill Norris or Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

SURGEON OPPORTUNITY. Immediate opening for General Surgeon in rural Nebraska. BC/BE. Must be licensed in Nebraska. Excellent benefits. Great hunting and fishing. Wallace & Panzer, MD, PC, 807 N. Ash St, Gordon, NE 69343; 1 (308) 282-1164.

SACRAMENTO. General Internist with or without subspecialty for busy, well-established Internal Medicine group. Send CV to David H. Lehman, MD, 2801 K St, Ste 520, Sacramento, CA 95816.

CALIFORNIA. BE/BC Internist to join staff of eight Internists in 14 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to Frank Kelley, MD, Kaweah Medical Group, 222 W. Willow, Visalia, CA 93291.

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SEATTLE, WASHINGTON. Outstanding opportunity to join multispecialty group practice. Full spectrum Family Practice with Obstetrics, associated with 250 bed hospital. Excellent financial package including guaranteed salary, benefits, interviewing and relocation expenses paid. Address inquiries to Dr Rockwell S. Fredrickson, Pacific Medical Center North, 10416 5th Ave NE, Seattle, WA 98125.

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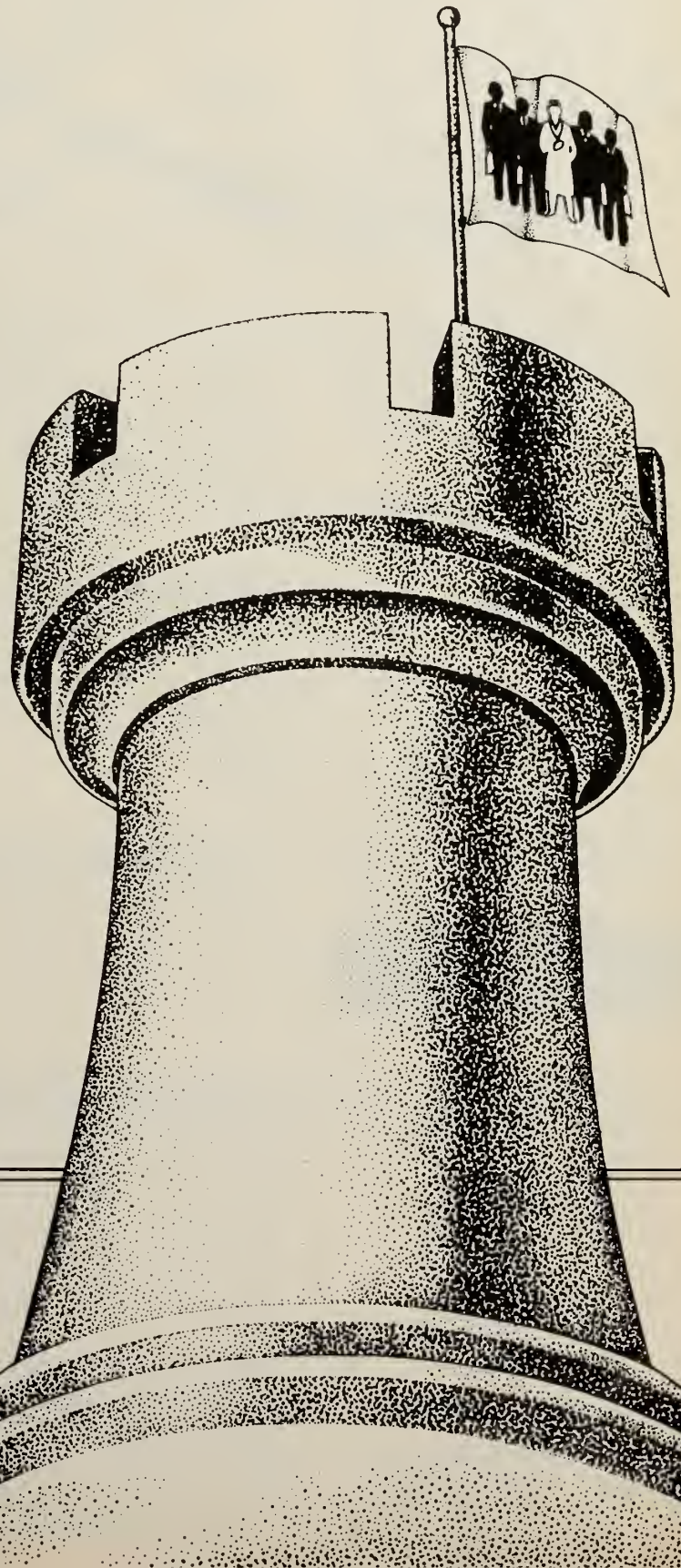

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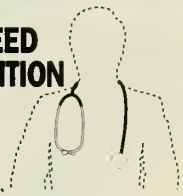

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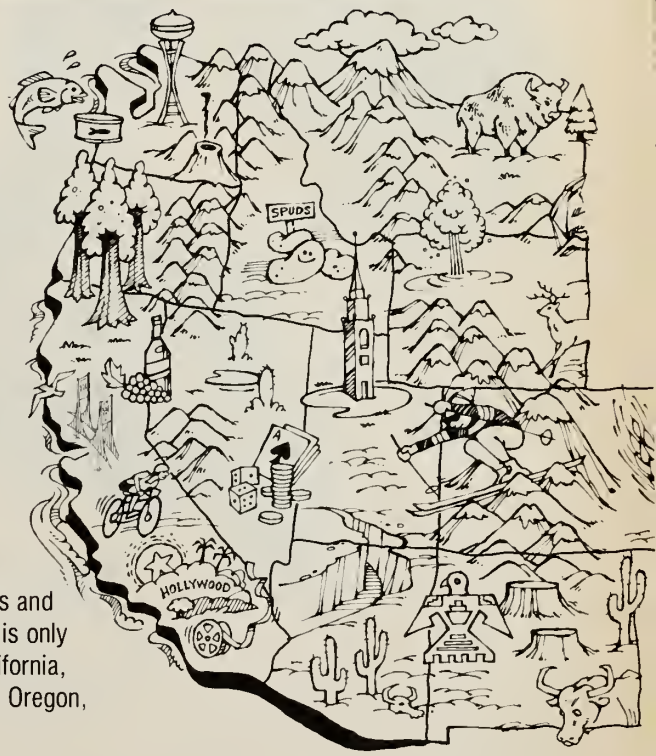

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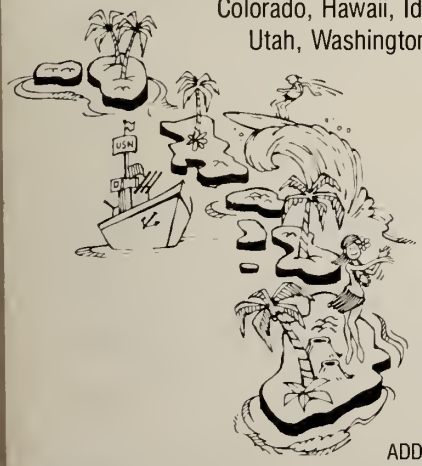

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New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 11-14, 1989, Holiday Inn Pyramid, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1988, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1989, date and place to be announced.

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Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, e.g., impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).

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Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. *Mutagenesis:* Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination, concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. *Impairment of Fertility:* No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

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Nursing Mothers: See CONTRAINDICATIONS section.

Pediatric Use: Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).** *Hematologic:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. *Allergic Reactions:* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periarteritis nodosa and systemic lupus erythematosus have been reported. *Gastrointestinal:* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. *Genitourinary:* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. *Neurologic:* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. *Psychiatric:* Hallucinations, depression, apathy, nervousness. *Endocrine:* Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. *Respiratory:* Pulmonary infiltrates. *Musculoskeletal:* Arthralgia, myalgia. *Miscellaneous:* Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN: *Usual adult dosage* for urinary tract infections is one DS tablet, two tablets or four teaspoonfuls (20 ml) *b.i.d.* for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis. *Recommended dosage for children* with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. *Renal Impaired:* Creatinine clearance above 30 ml/min, give usual dosage; 15-30 ml/min, give one-half the usual regimen; below 15 ml/min, use not recommended.

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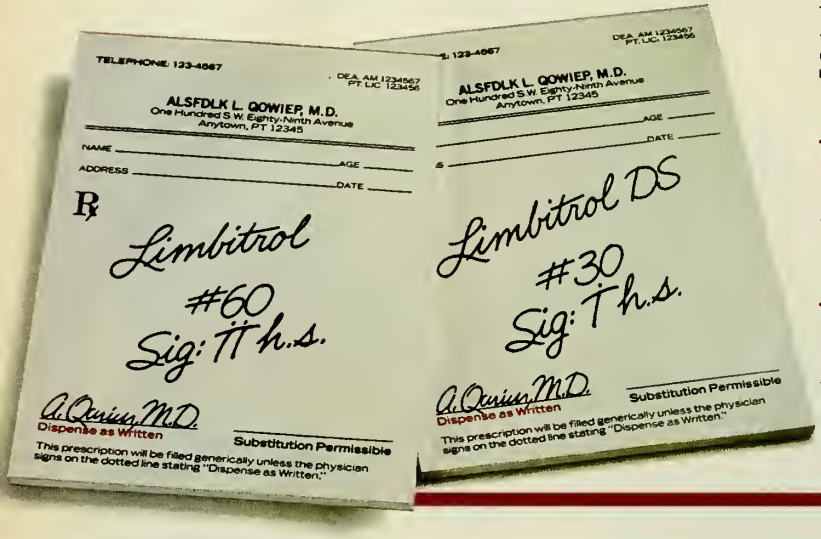

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References: 1. Data on file, Hoffmann-La Roche, Inc., Nutley, NJ. 2. Feighner VP, *et al: Psychopharmacology 61*:217-225, Mar 22, 1979.

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Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants; concomitant use with MAOIs or within 14 days of monoamine oxidase inhibitors (then initiate cautiously, gradually increasing dosage until optimal response is achieved); during acute recovery phase following myocardial infarction.

Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.**

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.
Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: *Cardiovascular:* Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric:* Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. *Neurologic:* Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns. *Anticholinergic:* Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. *Allergic:* Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. *Hematologic:* Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. *Endocrine:* Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other:* Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

How Supplied: *Double strength (DS) Tablets,* white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets,* blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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FELLOWSHIP First Mary A. Fraley Cardiovascular Surgical Research Fellow at the Texas Heart Institute, Houston

OUTSTANDING ACHIEVEMENTS Author of numerous articles, including "Indications for Early Bypass Grafting Following Intracoronary Streptokinase"; author of "The Female Surgeon—Dawn of a New Era," chapter in *A Century of Black Surgeons—The U.S.A. Experience*; Board of Directors, Association of Black Cardiologists; Secretary, Drew Society

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***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.

SQUIBB

Means a job well done.

We spend so much of our lives at work...it's no wonder our work performance is key to our quality of life. Work performance is also a key factor in assessing antihypertensive therapy. CAPOTEN improved hypertensive patients' work performance (e.g., ability to keep pace with the job, concentration, job satisfaction, less on-the-job fatigue).[1] So, for hypertensive patients who work, why not prescribe the antihypertensive that can work for them... CAPOTEN.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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The only H_2-antagonist indicated for the treatment of gastroesophageal reflux disease

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Zantac dramatically lessens pain of acid reflux[1] by inhibiting the formation of acid at its source—an action unique among pharmaceutical agents indicated for the treatment of gastroesophageal reflux disease.

Zantac® *Tablets*

ranitidine HCl/Glaxo

150 mg tablets bid

1 Sontag S, Robinson M, McCallum RW, et al: Ranitidine therapy for gastroesophageal reflux disease: Results of a large double-blind trial. *Arch Intern Med* 1987;147:1485-1491

Please see next page for Brief Summary of Prescribing Information

Glaxo/ ROCHE

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer, hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Glaxo

May 1988

Glaxo Inc.
Research Triangle Park, NC 27709

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Fresno, CA 93715.
or phone
(209) 442-3914. EOE.

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

December 3-4—**Annual Meeting of the Arizona Chapter of the American College of Surgeons.** Rancho de los Caballeros, Wickenburg. Sat-Sun. Contact: Lee Ansel, MD, Program Chairman, (602) 251-3131.

January 13-14—**Geriatrics in a Changing Society.** Scottsdale. Fri-Sat. Contact: Jean Kiernat, Institute of Gerontology, (602) 239-5844.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

January 27-28—**Coronary Heart Disease Update.** Embassy Suites Hotel, Scottsdale. Fri-Sat. Contact: Deborah Wilderson, Medical Education Resources, 1 (800) 421-3756.

January 27-29—**Mammography and the Search for Breast Cancer.** Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Tess Wade, Breast Clinic of Rochester, (716) 442-8969.

February 10-15—**Laser and Stent Therapy in Vascular Disease: International Congress II.** The Phoenician Resort, Scottsdale. Fri-Wed. Contact: Becky Bowman, Congress Coordinator, (602) 955-1000.

February 22-24—**12th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Phoenix OB/GYN Society, (602) 266-6321.

February 24-26—**Arizona Academy of Family Physicians Annual Scientific Assembly.** Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Shay Southwick, AzAFP, (602) 249-2021.

February 28-March 3—**Pediatric Update 1989.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Barbara Bengtson, Phoenix Children's Hospital, (602) 239-4350.

March 4-8—**Third Annual Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, Barrow Neurological Institute, (602) 285-3956.

March 9-11—**Current Management of Central Nervous System Tumors.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, (602) 285-3178 or 1-800-BARROW-1.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologist at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 29-February 3—**Clinical Update in Anesthesiology.** Tucson Hospitals Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray G. Atnikov, MD, c/o Box F110-63, Blaine, WA 98230. (604) 874-5291.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sat-Sun. Contact: Murray G. Atnikov, MD. (604) 874-5291.

February 27-March 2—**17th Obstetric Anesthesia Conference.** Dept of Anesthesiology Ohio State at Sheraton Waikiki Hotel, Hawaii. Mon-Thurs. Contact: Arlene Rogers, Ohio State University Hospitals, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 16-19—**Obstetrical Anesthesia: 1989.** UCSF at Hotel Meridien, San Francisco. Thurs-Sun. Contact: Anita Edgecombe, UCSF, C 450, Box 0648, San Francisco 94143-0648. (415) 476-2273.

CARDIOLOGY

January 19-21—**Cardiology 89: New Pharmacology, New Procedures, New Pacemakers.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott Hotel. Thurs-Sat. 16 hrs. $300. Contact: Nancy Donegan, Deverman & Associates, 7777 Alvarado Rd, Ste 280, La Mesa 92041. (619) 668-9091.

February 24-25—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Grand Hotel, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 10-11—**Risk Factors for Cardiovascular Disease: Lipids, Diabetes and Hypertension.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. $200. Contact: UCSF.

March 16-18—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Westin Maui Hotel. Thurs-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 31-April 1—**Coronary Heart Disease Update.** Medical Education Resources at Caesar's Palace, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

May 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Fisherman's Wharf. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

(Continued on Page 526)

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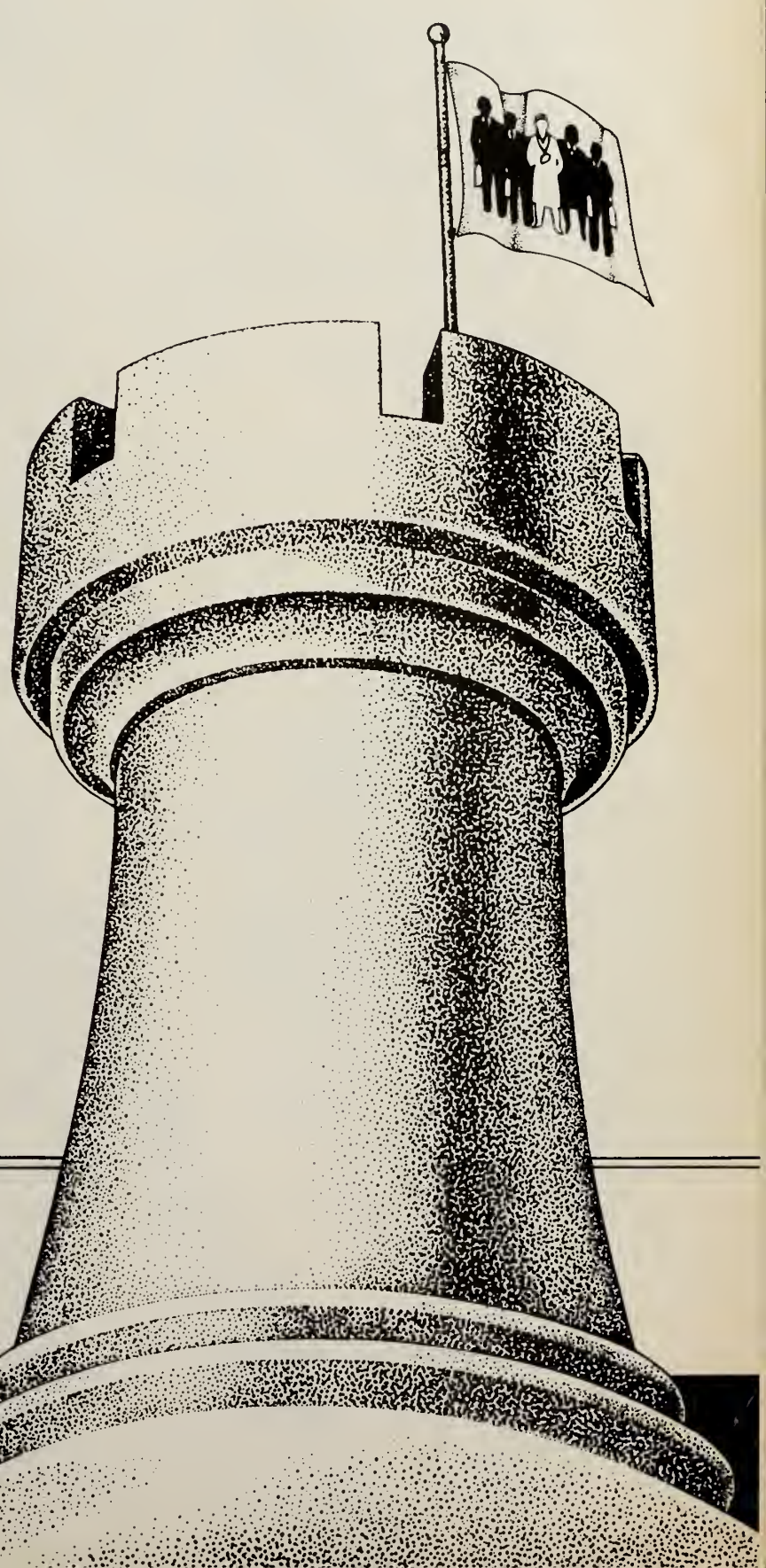

(Continued from Page 524)

June 16-17—**Coronary Heart Disease.** Medical Education Resources at Hyatt Lake Tahoe. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

EMERGENCY MEDICINE

December 4-9—**Current Concepts in Emergency Care.** Institute for Emergency Medical Education at Royal Lahaina Resort, Maui, Hawaii. Sun-Fri. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. (800) 524-5264.

December 5-9—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

January 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. $450. Contact: UCSD.

January 26-30—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Maui Marriott, Maui, Hawaii. Thurs-Mon. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

January 27-29—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

February 19-24—**Emergency Medicine.** UCD. Sun-Fri. Contact: UCD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

March 2-5—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Sheraton Universal, Los Angeles. Thurs-Sun. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

March 20-24—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. $450. Contact: UCSD.

May 1-5—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

November 16—**Common Musculoskeletal Problems.** VA Medical Center Sepulveda. 6 hrs. Contact: Arun J. Mehta, Rehabilitation Medicine Service (117), VA Medical Center, Sepulveda 91343. (818) 891-2473.

December 1-2—**Recent Advances in Occupational Cancer.** UCSF at Hotel Meridien, San Francisco. Thurs-Fri. $220. Contact: UCSF.

December 30-January 8—**Medical Acupuncture for Physicians: Part II.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. 10 days. 200 hrs. $3,200. Contact: UCLA.

January 6-7—**6th Annual Reider Laser Symposium—Urology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 19-20—**Third Urological Symposium.** Kenneth Norris Jr Comprehensive Cancer Center at Moseley-Salvatori Conference Center, Los Angeles. Thurs-Fri. 12 hrs. Contact: Louise B. Ball, Executive Secretary, PO Box J, South Pasadena 91030. (213) 680-2387.

January 21—**Innovations in Ankle Arthroscopy.** Mount Zion Hospital and Medical Center at Hyatt Union Square, San Francisco. Sat. 7.25 hrs. $275. Contact: Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

January 23-26—**Neurology Update.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Mon-Thurs. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 25-27—**12th Annual: Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wed-Fri. 21 hrs. $400. Contact: Edith S. Bookstein, NNN, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 8-10—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort, San Diego. Wed-Fri. 21 hrs. Contact: Bonny Mower, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 15-17—**22nd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15.5 hrs. $345. Contact: UCSF.

February 17-18—**Advances in Skin Cancer Management: A Multi-Specialty Approach.** UCSF at Ramada Renaissance Hotel, San Francisco. Fri-Sat. 10 hrs. $250. Contact: UCSF.

February 20-22—**Clinical Hematology and Oncology: 1989.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, Conference Coordinator. (619) 457-8556.

March 8-9—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn Union Square. Wed-Thurs. 14 hrs. $250. Contact: UCSF.

March 17-19—**Gastroenterology Update Cruise.** Center for Health Education at Queen Mary Hotel, Long Beach. Fri-Sun. Contact: Center for Health Education, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

March 21-24—**Topics in Rheumatology II.** Straub Foundation at Ilikai Hotel, Honolulu, Hawaii. Tues-Fri. 16 hrs. $350. Contact: Juliana J. Woo, MPH, Straub Foundation, 846 S Hotel St, #302, Honolulu, HI 96813. (808) 524-6755.

June 12-16—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

(Continued on Page 530)

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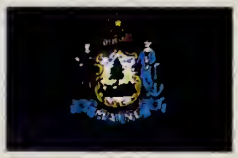

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CONTINUING MEDICAL EDUCATION

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OB/GYN

November 13-19—**11th Annual Review Course in Clinical Obstetrics & Gynecology.** The Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

November 14-15—**Gynecological Histopathology.** Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Tues. 12 hrs. $350. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

November 16-19—**Clinical Obstetrics and Gynecology.** Center for Health Education at Westin South Coast Plaza, Costa Mesa. Wed-Sat. 22 hrs. $450. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

January 6-7—**6th Annual Reider Laser Symposium—Gynecology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 16-20—**21st Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 38 hrs. $595. Contact: USC.

January 29-February 2—**Ob/Gyn.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

ORTHOPEDICS

December 8-11—**3rd Annual Fracture Management Symposium.** UCD at Hyatt Lake Tahoe. Fri-Mon. 18 hrs. $495. Contact: UCD.

January 21-28—**Orthopaedic Emergencies.** Scripps Memorial Hospital Encinitas at Kona Surf Resort, Kona, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 12—**1989 Interim Meeting of American Orthopaedic Society of Sports Medicine.** American Orthopaedics Society for Sports Medicine at Las Vegas, Nevada. Sun. Contact: AOSSM, 70 W Hubbard St, Ste 202, Chicago, IL 60610. (312) 644-2623.

PEDIATRICS

November 30—**Challenges in Perinatology: Are We Ready for the Future?** Perinatal Advisory Council of Los Angeles Communities at Sheraton-Universal Hotel, Universal City. Wed. 6 hrs. Contact: Marianne Gray, Executive Secretary. (213) 380-1790.

December 3—**Recent Advances in the Care of Children.** UCD at Hyatt Regency, Sacramento. Sat. 8 hrs. $125. Contact: UCD.

December 3—**7th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Educational Center, San Diego. Sat. 7 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 21—**Pediatric Cardiology for the Primary Care Physician.** Children's Hospital at Merritt Peralta Health Education Center, Oakland. Fri-Sat. 6 hrs. $75. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

January 27-29—**27th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott. Fri-Sun. 15 hrs. $225. Contact: Katherine Barky, MD, Childrens Hospital, PO Box 54700, Los Angeles 90054.

February 10-12—**Current Concepts in Pediatric Medicine.** Children's Hospital & Health Center at Marriott Hotel, San Diego. Wed-Fri. Contact: Children's Hospital & Health Center, Continuing Medical Education Office, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 20-22—**Pediatrics Update: 1989.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 24-25—**California Conference on Health Care for Foster Children.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 14 hrs. $125. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

March 9-11—**Brain Insults in Infants and Children: Diagnosis and Modern Management.** UCSD at Holiday Inn at the Embarcadero, San Diego. Thurs-Sat. 15 hrs. $325. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

March 17-18—**Hematology and AIDS: Neonatal & Pediatric Perspectives II.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 12 hrs. $160. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

PSYCHIATRY

November 18-20—**34th Annual Group Therapy Symposium.** UCSF. Fri-Sun. Contact: UCSF.

January 22-27—**15th Annual Midwinter Program for Psychiatrists: Special Focus on Panic and Anxiety.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $385. Contact: UCD.

January 27-29—**New Advances in Cognitive Therapy.** UCSD at San Diego Marriott Hotel and Marina. Fri-Sun. 16 hrs. $375. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

RADIOLOGY

December 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 13-15—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: R. Dawne Ryals, PO Box 920113, Norcross 30092-0113. (404) 641-9773.

January 19-21—**Duplex Imaging.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sat. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 21-22—**Workshop on Percutaneous Disectomy.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Sat-Sun. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 24-27—**MRI for Technologists—Symposium and Workshops.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Tues-Fri. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 27-29—**41st Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 21 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

January 31-February 4—**15th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Westin Kauai, Hawaii. Tues-Sat. 20 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 23-25—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Rancho Mirage. Thurs-Sat. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

SURGERY

December 1-4—**Bone Grafting: Biology and Application for Maxillofacial Indications.** Plastic Surgery Research Foundation at Le Meridien Hotel Coronado Bay, San Diego. Thurs-Sun. 21 hrs. $350. Contact: PSRF, PO Box 33387, San Diego 92103. (619) 692-9115.

December 3—**Reider Laser YAG & Argon Laser/Brachytherapy Symposium.** Center for Health Education, Long Beach. Sat. 9 hrs. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

December 3—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

January-July—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 13-14—**11th Annual Postgraduate Course: What's New in General Surgery.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

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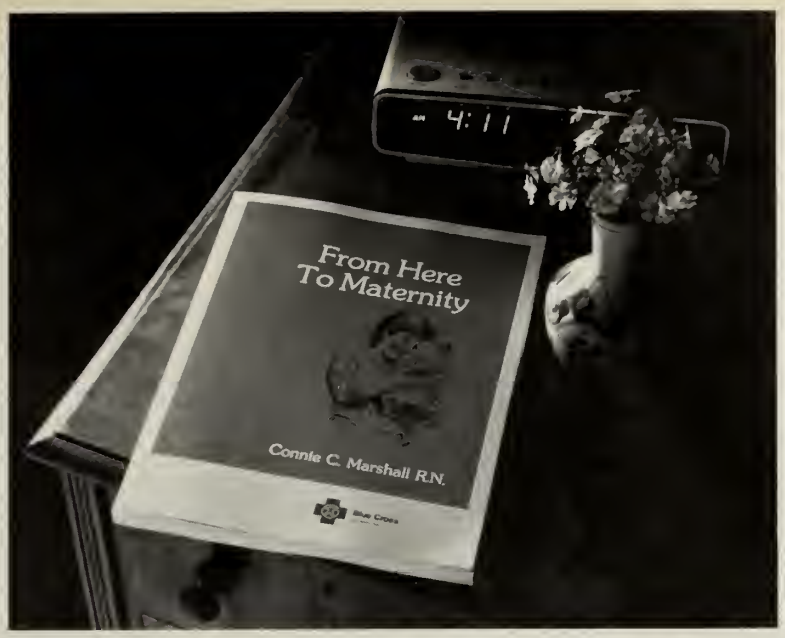

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Indications and Usage: *Hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone; in patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.*

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.*

Warnings: *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.*

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions: *The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.*

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions: *The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.*

Supplied: Capsules containing 25 mg. hydrochlorothiazide and 50 mg. triamterene, in bottles of 1000 capsules; in Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

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Bringing Medical Records Into The Twentieth & Twenty-first Century

Marshall B. Block, M.D.

After an extended vacation, my associate, who was covering for me, pulled me aside and said we must do something about our record keeping. Besides being difficult to read, the information needed to make medical decisions was difficult to find, and in some cases not recorded, making his job extremely difficult if not hazardous. I was somewhat taken aback and became defensive. I then reviewed several of my records. Indeed, it was difficult to follow what had transpired to the patient from visit to visit without my presence since a good portion of the clinical information was kept in my head and not in the patient's chart. After careful reflection, I decided that better medical records were needed, especially in the age of joint coverage and outside reviewers, and that our present system of record keeping was archaic.

Many physicians continue to keep medical records using handwritten notes containing abbreviations that are not universally accepted or understood. Furthermore, physicians have been notorious for having "poor penmanship." Every day records are sent from one physician to another and I am sure everyone has experienced the frustration of not being able to understand what had transpired during the patient's medical history. Some physicians make up for this deficiency by sending a summary letter, but many times all we receive are copies of progress notes which are illegible, unintelligible and non-sequential. Furthermore, our system of tracking laboratory data, radiological studies, surgical procedures, etc., is non-existent in most offices. The sheer number of laboratory slips which crossed our desks on a daily basis is overwhelming. Each office has developed a system to handle it but most systems lack specificity and reliability. How often have radiological reports been misfiled, not been seen or even never sent? How many of these are abnormal? How many need action? We are the last of the historians who use pen and pencil to record changes in our data-base. Lawyers have long ago moved to computerized word processing. Authors of novels as well as text books are all computerized. Accounting firms have moved to complete computerization of all of their data. Banks are even phasing out the human element, i.e. automated tellers. Why then has medicine not moved forward, and made the quantum leap to medical information computerization?

Previously, intermittent hospitalizations allowed for the recording of medical information in a typed fashion in the initial history and physical and discharge summary. However, with less patients being hospitalized and more studies being done in the out-patient arena, there has been less organization of medical information for each individual patient. Thus, when medical records are reviewed by an outside agent or agency the initial impression is one of total disorganization. Worse yet, a recent survey of out-patient facilities (our offices) has revealed a striking deficiency in the recording of the results of studies be they laboratory or radiological. Medical information must be organized in a meaningful way, not only for the initial recorder, but for all future "readers," be they other physicians or "significant others." Third party payors want to know what they are paying for and whether the bills that are sent are justified. Furthermore, they want to be certain that what is billed is actually done. I believe this desire for fiscal responsibility is not

continued on page Eight

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In This Issue

- From Our President
- New Dean
- Physicians in the News
- New Members
- Classified

From Our President

Richard L. Collins, M.D.

The effort to establish a program to assure the availability of medical care for Arizona's senior citizens is well underway, thanks to the leadership of a group of dedicated physicians and community leaders.

The V.I.P.* (*Very Important Patient) Program Committee has agreed upon recommended guidelines for a demonstration project and authorized a search for funding to begin.

The program is designed for that group of Medicare participants whose incomes are too great to allow them to receive medical services through the Arizona Health Care Cost Containment System (AHCCCS) but too limited to fund food, clothing, shelter AND medical care.

Too many members of this group have been doing without food or electricity in order to pay their doctor bills--or have been doing without medical care altogether. I am pleased that we are now doing something substantial to eliminate the need for such choices.

The challenge is to identify the members of this group and qualify them as participants in our V.I.P.* Program and then connect them with nearby physicians who are also program participants.

Physicians who take part in our V.I.P.* Program will accept V.I.P.* patients at Medicare rates, whether or not the physician is a participant in Medicare. According to a survey conducted last spring by ArMA staff, 47% of our members were enthusiastic about this concept, 45% were interested and wanted further information and only 8% were opposed. Although we certainly would like 100% support from our members, we were pleased that the negative component was at the single-digit level. It says a lot for the physicians of this state that the vast--even overwhelming--majority of them were supportive.

The committee's recommendations included (which will not become ArMA policy until reviewed and approved by the Board of Directors)

- Participants should have a household income above the AHCCCS eligibility level and below $10,000;
- All Medicare participants whose incomes fit in this category will be eligible to participate in the ArMA V.I.P.* Program;
- Screening patient participants will primarily be done by mail with complex cases screened in person by professional caseworkers. Confidentiality will be a critically important part of all screening processes.
- Any waivers of Medicare co-payments and deductibles must be done on a case-by-case basis by individual physicians.

A lists of foundations which are interested in medical or social programs and are either located in Arizona or have funded Arizona projects has been compiled. The foundations are being contacted to see if they are interested in the ArMA V.I.P.* project. Funding is needed to hire professional caseworkers and administrative staff to oversee the program.

We will keep you informed as the V.I.P.* program develops and hope you will join us in providing medical care for this group which so definitely needs your help ❑.

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Medical Teaching As Andragogy

A centuries-old tradition in teaching is being called into question, not by modern technology but by more contemporary assumptions about teaching and learning. Most of our current teaching was adapted from the monastic schools of Europe in the seventh and twelfth centuries. Developed from observations of monks teaching groups of very young children to read and write, this form of teaching has been given the label pedagogy. The term is derived from the Greek words *paid* and *agogus* meaning to lead or teach children. The practices underlying this form of teaching are with many of us today.

In pedagogy the learner is considered dependent on the teacher and the teacher is expected to take full responsibility of what is to be learned, when it is to be learned, how it is to be learned and if it has been learned. Pedagogy assumes that learning is a process of acquiring subject-matter content until it has been mastered. Individual learners are considered to be more similar than different and are therefore taught a common curriculum. The pedagogical curriculum contains subject-matter that promises to become useful in later life. Pedagogy considers direct instruction from the teacher to be essential and the learners prior experience to be of little or no value.

The pedagogical model, the one we use in most of our teaching, is in need of some much belated renovation. The assumptions underlying this widespread approach to teaching are coming into question. They are being questioned not because they are faulty but rather because they are inadequate as a basis for the teaching challenges of today.

Pedagogy is intended to transmit knowledge and skills that would stand the test of time. This is rarely the case in medicine where critical information can have a six month half-life and lifesaving technology eclipses itself quarterly. It is an approach to teaching that welcomes the learner tabula raza. Many of today's medical students come with advance degrees and substantial experience in medicine or in other professional fields. The pedagogical approach expects the learner to fill their reservoir of knowledge and to draw upon it throughout life. In medicine this is rapidly being replaced by the acknowledged need for continuing, lifelong inquiry.

Cyril O. Houle is credited with being the first to investigate the assumptions underlying the widespread and exclusive use of pedagogy. In "The Inquiring Mind" Houle described adult learning as a natural process, a personal pursuit resulting from a set of common factors. The label *andragogy;* based upon the *Greek aner* meaning man, not boy; is used to describe the leading or teaching of adults. Adulthood is defined as the point at which individuals perceive themselves as essentially self-directed. For the many medical students this point is reached several years prior to medical school. The andragogical approach favors learner independence over dependence, learner self-direction over teacher direction, the use of learners' experience over ignoring it, and the demonstrated utility of subject matter over promises of future worth.

In andragogy the learner is seen as an adult moving from dependency to increasing self-directedness. The teacher is seen as responsible for encouraging and nurturing this movement. Andragogy assumes that the learner sees education as a process of developing increased competence in dealing with a range of life's challenges. Teaching in andragogical settings is inherently more collaborative. Learners come to the learning setting with an agenda of real-life tasks and problems and can benefit fully from conditions and procedures that will help them discover what they need to know. Each learner's experience is available as a rich resource for him/her as he/she gains meaning from the learning of others. Subject matter is seen, in andragogy, as diffuse, dynamic and ever changing. The curriculum must also include skills in learning how to learn and seeking knowledge for its own sake.

Though andragogy will not soon replace pedagogy as the dominant teaching model in general education, it is being welcomed as an approach to working with adult students, those who are intent on the accomplishment of clear cut goals, who desire to be actively involved in their learning, and who seek knowledge for its own sake. Andragogy may also deserve our consideration as an approach to medical teaching.❑

Robert F. Rubeck, Ph.D.
Assistant Dean for Medical Education
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1988 Taxable Equivalent Yield Table for Arizona

Taxable Income (000)		Combined Federal/State Tax Brackets	Tax-Exempt Yield Equivalents								
Single Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
$17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
Over $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

There is no assurance that state tax rates will remain unchanged. When two state brackets fall within a federal bracket, the higher state bracket is combined with the federal bracket. The state tax rates assumed do not take into account possible adjustment of tax brackets based on changes in the Consumer Price Index.
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New UA Medical School Dean

James E. Dalen, M.D.

An academic scholar with a clear focus on the big picture, the new dean of the College of Medicine at the University of Arizona faces monumental challenges in building image, staff and facilities. He wants to clarify the college's mission. Five major department heads need to be hired; five construction projects need to be completed.

These are challenges that might give pause to any new administrator. But after just four months to get his feet on the ground, the new Vice Provost for Medical Affairs and Dean of the College of Medicine, James E. Dalen, M.D., faces them with anticipation and even enthusiasm as he begins to carve his mark on the university landscape.

"Our first and most important responsibility is to serve the entire state," Dr. Dalen said. "This is not just Tucson's medical school -- it is Arizona's medical school. We should be the primary resource for the entire Arizona medical community."

Part of that effort is working closely with the teaching hospitals in Phoenix, he said. "I hope to establish an associate dean in Phoenix."

The dean's responsibility in shaping the college's role in the state is one of oversight, Dr. Dalen said. "All of the department heads who work with me have specific areas of responsibility, individual areas they care about and work for. It is my job to be concerned about the entire operation, to have the overview, set priorities and reinforce attitudes and recruit the right people."

Recruiting will be a top priority as a nationwide search continues to find department heads for the college's departments of physiology, obstetrics and gynecology, psychiatry, surgery and pathology.

"What we do (in recruiting and hiring so many department heads) will determine the future course of the medical school. Department heads tend to serve for 10 to 20 years, so it is imperative that we recruit the right people," he said.

Dr. Dalen is already reviewing applications but expects it will take about a year to get all five positions filled with the right people.

At the same time, five major construction projects still need funding and supervision. One of the strengths of the university and the College of Medicine is the backing it gets from the community, Dr. Dalen noted.

"I was surprised when I arrived to find out how extensively the people of Arizona support the school. The amount of private philanthropy we receive is unusual, compared with other state medical colleges around the country."

That support is particularly appreciated, he said, in light of another unusual situation: the Arizona legislature does not fund building construction. The operating budget of the state medical school is provided by state taxes, but if the College of Medicine needs facilities, it is up to the school to find its own funding.

Closest to gound breaking is the expansion of the library, which at present serves the entire health sciences center: the colleges of medicine, pharmacy and nursing. When the expansion is complete, the library data base will be on-line with all the major medical facilities in the state. This will give physicians statewide access to the information in the health sciences library.

Ground breaking should take place within a month for the new life sciences center, which will serve both the medical school and the main university. Fundraising is about halfway complete for the proposed children's research center and is just beginning for a planned cardiac center similar to the university's cancer center. The final project is a new ambulatory care facility which will replace the presently overcrowded clinics operated by the medical school.

"Obviously, I can't take credit for starting any of these projects," Dr. Dalen said, "but it is my job to make sure they get finished."

It was the many strengths of the College of Medicine that attracted him to Arizona, he said. "I was impressed with the relationship between the medical school and the main university."

Like so many other facets of the university's personality, that, too, was unusual, he noted. "It is common for many medical schools to be separated both geographically and politically. Not only are they located apart from the main campus but it is common that the medical school and the main university have different interests."

At the University of Arizona, however, there is strong collabora-

Faces Challenges with Zeal

tion between the faculty of the College of Medicine and the main campus.

Additionally, he said, there is a strong commitment to teaching and innovations in teaching are given high priority.

"Any successful College of Medicine has three functions," Dr. Dalen said. "There must be a strong commitment to teaching, but there also must be an aggressive research program and an effective clinical program."

The College of Medicine has one of the strongest research programs in the nation -- it is in the top 20 in research dollars -- and last year alone it devoted $48 million to research projects, he said. The clinical function needs expanding, however, and that is what much of the construction program is designed to accomplish.

One problem facing Arizona's medical school is diminishing enrollment. Although applications did not diminish four or five years ago when they started dwindling in eastern medical schools, the drop-off has finally begun to affect this state.

"Although we did have fewer applications this year than in years past, we still had plenty to assure a quality class," Dr. Dalen said. "We had 230 applications for 88 positions, so the class size this year did not decrease."

The college administration often does not know exactly who will attend until the last minute -- some students who are accepted decide to go to medical schools in other parts of the nation. In order to maintain the highest quality in the student body, Dr. Dalen would like to establish academic scholarships to keep the best students in Arizona.

At the other end of the academic process, Dr. Dalen would like to look at extending the structure of anesthesia residencies into other specialty areas. In the Department of Anesthesia, all residents are in one coordinated program: they spend time at Maricopa Medical Center where they experience a high percentage of trauma and obstetrical cases; at University Medical Center where they spend much of their time with cardiology cases; and at St. Joseph's Hospital and Medical Center, Phoenix, with neurosurgery cases.

"This gives them broader experience than they would receive at only one medical center," Dr. Dalen said. "This approach may be appropriate for other specialties."

Dr. Dalen, 56, is a native of Seattle. After serving in the U.S. Navy during the Korean War, he received his B.S. degree with highest honors from Washington State University in 1955. He received an M.A. degree in Psychology from the University of Michigan in 1956 and his M.D. degree from the University of Washington in 1961. In 1972, he received a M.S. degree in Public Health from Harvard University.

He completed his internship and residency in Internal Medicine at Boston City Hospital and the New England Medical Center. He then served a three year fellowship in Cardiology at the Peter Bent Brigham Hospital. After completing his training, he was a member of the faculty of Harvard Medical School from 1967 to 1975, where he was Associate Professor Medicine.

He joined the faculty of the University of Massachusetts Medical School in 1975 as Professor of Medicine and Chairman of the Department of Cardiovascular Medicine. In 1977, he became the Chairman of the Department of Medicine and Physician-in-Chief of the University of Massachusetts Medical Center. He served as Acting Chancellor of the University of Massachusetts at Worcester from July 1986 until August 1987. In May of 1988 he accepted a position at the University of Arizona as Vice Provost for Medical Affairs and Dean of the College of Medicine.

In addition to his clinical activities, Dr. Dalen has been active in cardiovascular research. He has served as principal investigator of many clinical trials sponsored by the National Institutes of Health. He has published extensively and is co-author of several textbooks.

He serves on the editorial board of the Journal of the American Medical Association and several other medical journals and is the Editor of the Archives of Internal Medicine. He has served as President of the American College of Chest Physicians, President of the New England Cardiovascular Society, and Governor for Massachusetts of the American College of Physicians and the American College of Cardiology.

Dr. Dalen received the Outstanding Clinical Educator Award at the University of Massachusetts Medical School in 1981 and in 1982. He was selected as Teacher of the Year of the Department of Medicine in 1982. In 1987 he received the Distinguished Public Service Award from the University of Massachusetts. In 1988 he was named the University of Washington Distinguished Medical Alumnus of the Year.

In his spare time, Dr. Dalen likes to jog, swim, hike and ski cross country. He likes American colonial, French impressionist and "some" Spanish art and is only one course away from another Master of Arts degree in art history.❑

continued from Page One
unreasonable. Unfortunately, our credibility is being questioned and as much as we detest this erosion, third party payors are going to continue to scrutinize our records. Because of this intensified review of our records, a more concise, critical record keeping approach is essential. The problem oriented record appears to this writer to be the only one that will be able to be universally accepted and I believe is the starting point for the complete computerization of medical records.

The development of a "scanner" which can transfer information from a typewritten page to a computer disk will be the next step in the computerization of our old records. By using the "S.O.A.P." record keeping method, universal understanding of the patient's problems can be finally brought to fruition. Using a "typed" format either by standard typewriter or word processor will further enhance the universality of our historical records. In the future, voice recognition will permit the direct transmission of our voice to the computer without the interface of a printed record. Transcribers will no longer be necessary as the spoken word will appear on a CRT screen immediately. Systems such as these already are in place at various radiological facilities, and with technological improvement should be available for internal medicine practices within the near future. Thus, I predict that within the next five years, we will have the capability of completely computerizing all of our medical records and tracking all of our outside data. We probably will not have a paper system, but rather we will all have CRT terminals at our desks and at our homes which will make for better patient care.

The first step in this major transformation of medical record keeping rests with us. We must make the attempt and effort to begin the process of transforming haphazard record keeping to a systematic organized format following the problem oriented approach. The next step, full computerization, will then be easy to make. We must start accepting the challenge and enter the Twenty-first Century. ❑

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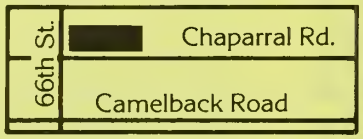

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of Medicine - 1982
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Medical School - 1973
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Suite 109, Tucson
Wayne State University
School of Medicine, Detroit - 1978
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Tucson
University of Arizona
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Associate

Maricopa

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Cardiovascular Diseases
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Harvey A. Turner, M.D.
General Surgery
7920 E. Coronado Road
Scottsdale
Medizinische Fakultat
Der University Bern - 1959

Pima

Ira H. Tepper, M.D.
Gynecology
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Tucson
State University of New York
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Physicians In the News

Donald L. Damstra, M.D.

Donald L. Damstra, M.D., has joined the Arizona Medical Association on a full-time basis as Assistant Executive Vice President-Physician's Health Committee, according to Executive Vice President Bruce E. Robinson.

Dr. Damstra, who earned his medical degree at Northwestern University's School of Medicine, has been with ArMA on a half-time basis for two years and is responsible for the establishment of the Physician's Health Program for physicians impaired by alcohol, drugs or emotional stress.

For 19 years prior to his work with ArMA, Dr. Damstra served as Medical Director of the Alcohol and Drug Treatment Program at St. Luke's Medical Center. During the past two years, Dr. Damstra has been senior consultant to the drug and alcohol treatment program at St. Luke's.

Working full-time with the medical association will allow him to become more personally involved with physicians in the program during the course of their therapy, Dr. Damstra said. "I will have extended responsibilities for monitoring the recovery of physicians who have completed the therapeutic portion of the program."

Additionally, Dr. Damstra said, he will work with the Physician's Health Committee to develop other programs to assist physicians in Arizona. Some of the programs will deal with specific needs such as aging and retirement, the stress of changing a medical practice and the effects of stress in general.

A final area Dr. Damstra is concerned about is the quality of general medical care that physicians receive. "We're going to look at ways to possibly improve the quality of care physicians get," he said.

Local Physicians Represent Experts at National Conference

Ronald B. Joseph, M.D.

Two members of the medical staff at Humana Hospital -- Phoenix participated as experts in their field at the national conference of the American Association for Hand Surgery in Toronto, Canada in October.

Ronald B. Joseph, M.D. and Leonard S. Bodell, M.D., founders of the Arizona Institute for Hand and Plastic Surgery, Scottsdale, participated as faculty and presentors at the conference, which hosted an estimated 1500 medical specialists.

Dr. Joseph presented a paper which he co-authored with Dr Bodell entitled, "Painful Dysfunction Relief of the Thumb CMC Joint with the Eaton Prosthesis. to fellow hand surgeons at a scientific session.

Leonard S. Bodell, M.D.

Dr. Bodell served as faculty on an expert panel, responding to questions from colleagues regarding complex surgical cases. He also presented information on "Rheumatoid Arthritis Hand Reconstruction" during a state-of-the-art mini-course.

In the paper co-authored by the physicians, the result of research was presented regarding patients who received an Eaton prosthesis for thumb base arthroplasty, or joint replacement. The procedure resulted in an overall decrease in pain, increased function and strength, and increased stability of

the joint. The research project was done with 376 patients, all of whom has some form of arthritis.

Dr. Joseph and Dr. Bodell specialize in hand, upper extremity and arthritis surgery; shoulder reconstruction; arthroscopy, peripheral nerve surgery; and microsurgery reimplantation. Their medical associates at the Institute include an additional orthopedic surgeon, a plastic surgeon, two neurologists and two psychologists.

Samuel J. Hessel, M.D., of Scottsdale, was named as a fellow of the American College of Radiology (ACR), during ceremonies at the ACR annual meeting in Cincinnati, Ohio. Selected for his outstanding contributions to the field of radiology, Dr. Hessel was named as one of 136 new fellows by the College's Board of Chancellors.

Fellowships in the College are awarded for significant scientific or clinical research in the field of radiology, or significant contributions to its literature. Criteria for selection also include performance of outstanding service as a teacher of radiology, service to organized medicine and an outstanding reputation among colleagues and local community as a result of long term superior service.

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Epidemiology of Inflammatory Bowel Disease in a Defined Northern California Population

ROBERT A. HIATT, MD, *and* LEON KAUFMAN, MD, *Oakland, California*

The epidemiology of inflammatory bowel disease is described among the more than 1.5 million members of the Kaiser Permanente Medical Care Program (KPMCP) in northern California. We reviewed a 20% random sample of the medical records of 2,067 persons first admitted to hospital in the period 1971 through 1982 with codes indicating inflammatory bowel disease. We also examined all new outpatient cases for a 1-year period from records at the Oakland KPMCP facility. Criteria used to establish valid cases adhered to standards used in previous studies but were revised to reflect current diagnostic methods. The disadvantages of using hospital discharge data have been identified and quantified. In this population, only 21% of ambulatory patients with inflammatory bowel disease were admitted to hospital in a 3½-year period. There was no difference in the incidence of the disorder by sex or between whites and blacks, but it was rare in Asians. A bimodal age distribution was suggested for Crohn's disease but not for ulcerative colitis. During the 12 years of this study, rates of hospital admissions for ulcerative colitis decreased and for Crohn's disease were slightly increased.

(Hiatt RA, Kaufman L: Epidemiology of inflammatory bowel disease in a defined northern California population. West J Med 1988 Nov; 149:541-546)

The etiology of inflammatory bowel disease is not known. Epidemiologic studies of the incidence of this group of disorders have been useful in suggesting the causes,[1] but such investigations have been hampered by problems with the data available on inflammatory bowel disease. Two of these are the difficulty of generalizing results from individual studies and the definition of the disease. In this country, although a few community studies have been reported,[2,3] most have been limited to studies of patients from tertiary centers or to patients in hospital.[4-6] Because many patients with inflammatory bowel disease have relatively mild symptoms and are never admitted to hospital, these studies misrepresent and underestimate the true incidence in a community. In reports from Europe, which include both inpatients and outpatients and indicate that access to health care systems is usually evenly distributed, criteria for the diagnosis of the disorder lack uniformity. This sometimes results in the inclusion of acute self-limited disease, probably infectious in nature, and leads to an overestimation of the actual incidence of inflammatory bowel disease.[7-11]

In this study, we have examined cases of inflammatory bowel disease in the members of the northern California Kaiser Permanente Medical Care Program (KPMCP), applying strict diagnostic criteria to both inpatient and outpatient medical record sources. We were interested in the nature and magnitude of the imprecision of the hospital inpatient data and in the comparison with outpatient data in a subset of the same population.

Methods

Population at Risk

There were 1,704,322 members of the KPMCP in northern California in 1980. The health plan membership was demographically similar in age, sex, race, and income to the population enumerated by the United States census in the San Francisco Bay Area.[12] Members of this prepaid health plan have access to a full range of medical inpatient and outpatient services at 14 hospital facilities and 23 outpatient clinics throughout the San Francisco Bay and Sacramento (California) areas.

Data Resources

Hospital discharge records from all facilities within the northern California region, which were computer-stored from 1971 through 1982, were searched for a diagnosis of inflammatory bowel disease. Specifically, codes 563.0 (regional enteritis), 563.1 (ulcerative colitis), 563.9 (other chronic colitis), and 569.0 (proctitis) were extracted for the period 1971 through 1978 (*International Classification of Diseases, Adapted* [ICDA], eighth edition), and codes 555.0 through 555.9 (regional enteritis) and 556 (idiopathic proctocolitis) were extracted for the period 1979 through 1982

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ABBREVIATIONS USED IN TEXT

ICDA = *International Classification of Diseases, Adapted*
KPMCP = Kaiser Permanente Medical Care Program

TABLE 1.—*Diagnostic Criteria for Inflammatory Bowel Disease**†

Ulcerative Colitis

Definite

History of diarrhea or rectal bleeding or both for 6 wk or more; with

Either a record of at least one sigmoidoscopy or colonoscopy revealing one or more of the following: friability of the mucosa with contact bleeding, or petechial hemorrhages, or ulceration with intervening inflammation of the mucosa; or a barium enema with radiologic evidence of ulceration or narrowing or shortening of the colon; or characteristic macroscopic and microscopic changes in a specimen obtained by surgical resection, biopsy, or at autopsy

Probable

An acceptable sigmoidoscopy, colonoscopy, or barium enema report but inadequate history

Characteristic macroscopic appearance of operative or postmortem specimen, but histology indefinite

Possible

An acceptable history but sigmoidoscopic or colonoscopic appearances dubious—for instance, mucosal erythema only or any of the changes described above but qualified as doubtful—and no barium enema, or

An adequate history but barium enema findings dubious—such as loss of haustration only—and no sigmoidoscopy or colonoscopy report, or

A medical record with a discharge diagnosis of ulcerative colitis, no findings inconsistent with the diagnosis, and an acceptable history

Ulcerative Proctitis

Definite

The criteria were as for definite ulcerative colitis, with evidence that normal bowel was visible above the affected rectal mucosa on sigmoidoscopy or colonoscopy

Probable

The criteria were as for probable ulcerative colitis, with normal mucosa visible above the affected rectum on sigmoidoscopy or colonoscopy, or where changes on barium enema did not extend above the rectosigmoid junction

Possible

A medical report with a discharge diagnosis of ulcerative proctitis, no findings inconsistent with the diagnosis, and an acceptable history

Crohn's Disease (regional enteritis)

Definite

A characteristic positive histologic report from an operative or autopsy specimen

Probable

A laparotomy report of characteristic macroscopic appearances of the small bowel but no specimen of gut resected for histology, or

An equivocal histologic report from an operative specimen with characteristic macroscopic features, or

A colonoscopic report compatible with Crohn's disease and biopsy specimen with features strongly suggestive of Crohn's disease, or

A radiologic examination strongly suggestive of intestinal or colonic inflammatory disease with obstructive or fistulous features

Possible

A medical record with a discharge diagnosis of Crohn's disease, regional enteritis, or granulomatous colitis; no findings, clinical or radiologic, inconsistent with the diagnosis; and an acceptable history

*Adapted from Garland et al.[5]

†Note exclusion criteria: Symptoms of enteritis or colitis for less than 6 weeks' duration or associated with specific infections—such as *Campylobacter—Clostridium difficile* toxin, radiation therapy, or ischemia.

(ICDA, ninth edition). There is no exact equivalence available for the two editions of the coding system, but, for this study, ninth edition codes were translated back into eighth edition codes: codes 555.0 through 555.9 were considered equivalent to 563.0, and code 556 was considered equivalent to 563.1. For calculations that involve unvalidated counts of ulcerative colitis, we used only code 563.1 because most of the cases coded as 563.9 and 569.0 were not ulcerative colitis.

The incidence of a first hospital admission in the 1971-1982 period was calculated on the basis of midyear health plan membership figures for each year. Rates were age-adjusted to the 1970 US census population by the direct method[13] to make them comparable with other studies. Inherent in this rate, however, is the possibility that persons admitted to hospital before 1971, and therefore not in our hospital records file, were counted as "first hospital admissions" on subsequent admissions in the 1971-1982 period. This would be especially the case in the earlier years after 1971. To obviate this problem when examining trends, we calculated a rate for the number of persons admitted to hospital in any single year per midyear membership.

Validating Hospital Discharge Diagnoses

To ascertain the validity of diagnoses obtained from the computer-stored hospital discharge file, one of us (L.K.) reviewed a randomly chosen sample of 396 (about 20%) of the 2,067 persons admitted to hospital in the 1971-1982 period with a presumed diagnosis of inflammatory bowel disease. This review followed criteria previously used by others in epidemiologic studies to categorize cases as definite, probable, possible, or not inflammatory bowel disease.[5] These criteria were modified to reflect current diagnostic methods (Table 1). Thus, diagnoses of the disorder that were associated with specific infections—such as *Campylobacter—Clostridium difficile* toxin, radiation therapy, ischemia, or symptoms that lasted less than six weeks (that is, probably infection) were excluded. In addition to whether or not the case fit our diagnostic criteria, we sought information on the race, date of first diagnosis, and whether or not a person was admitted primarily because of inflammatory bowel disease or because of some other illness.

Outpatient Data

We used outpatient data from records of the gastroenterology clinic at the Kaiser Permanente Medical Center, Oakland, facility, which in 1980 served a population of 156,113. It is the practice in the Oakland facility for all patients thought or known to have inflammatory bowel disease to be referred to a gastroenterologist; each of the four gastroenterologists in the department maintained a card file. For the one-year period July 1980 through June 1981, medical records of outpatients with the disorder were reviewed using the same criteria as for the inpatient records. Additional incident cases from Oakland, representing persons directly admitted to hospital, were sought by reviewing the records of all patients with inflammatory bowel disease admitted there in the 1980-1981 period. To determine the number of incident cases of subsequent hospital admissions for inflammatory bowel disease, we cross-matched the outpatient cases with the hospital discharge files of all northern California Kaiser Permanente facilities through the end of 1984.

Results

Hospital Discharge Data

In the period from 1971 through 1982, a total of 885 persons were discharged with a diagnosis of Crohn's disease, and 985 were discharged with either ulcerative colitis or ulcerative proctitis. The mean annual age-adjusted rates of first hospital admission in that period were 5.20 per 100,000 for Crohn's disease and 5.47 per 100,000 for ulcerative colitis. Rates per 100,000 population were slightly higher among women for Crohn's disease (5.65, versus 4.68 for men) and were similar among the sexes for ulcerative colitis (6.30 for women and 6.33 for men). The age-specific rates of first hospital admission for Crohn's disease had a bimodal curve showing peaks in the age groups for 20 to 29 years and for 60 to 69 years (Figure 1). For ulcerative colitis, the frequency of hospital admissions rose rapidly until the age group 20 to 29 years, plateaued for the next ten-year age group, and continued a substantial upward trend into the highest age groups (Figure 2).

Time trends indicate that hospital admissions for Crohn's disease have increased slightly during this 12-year period, whereas rates for ulcerative colitis have decreased (Figure 3).

Validating Hospitalized Cases of Inflammatory Bowel Disease

We were able to review 381 (96%) of the 396 randomly chosen medical records. The others were either not located or there was too little information to say whether or not a person had inflammatory bowel disease. Of reviewed records, 75% were judged to reflect definite (257 records) or probable (29 records) inflammatory bowel disease. Nine (2%) cases were classified as only possible disease and not used in any of the analyses that follow. A total of 86 (23%) were misclassified as having inflammatory bowel disease (Table 2). As expected, most misclassifications were closely related gastrointestinal diseases. Valid cases of the disorder were confirmed from 84% of hospital discharges coded as either 563.0 or 563.1 but only 28% of those coded as 563.9 or 569.0.

Misclassification also occurred between diagnoses. Of cases coded as Crohn's disease, 2% were ulcerative colitis, whereas 10% of cases coded as ulcerative colitis were Crohn's disease.

In the age group over 80 years, the number of cases of disease was small. For ulcerative colitis, because of the pronounced increase in the rate of hospital admissions among the older groups, we elected to review all available records of persons older than 70 years. In comparison with the original random sample for the over-70-years group, the proportion accurately diagnosed as having ulcerative colitis in the ex-

TABLE 2.—*Diagnoses of Hospitalized Cases Miscoded as Inflammatory Bowel Disease From Sample of 381 Persons, KPMCP, Northern California*

Diagnosis	*Cases, No.*
Self-limited gastroenteritis or colitis, such as infectious disease	25
Irritable bowel syndrome	8
Radiation enteritis, proctitis	8
Diverticulitis	4
Appendicitis	6
Other diseases	35
Total	86

KPMCP=Kaiser Permanente Medical Care Program

Figure 1.—The graph shows age-specific rat s of first hospital admission in 1971-1982 for 885 persons with Cr hn's disease, Kaiser Permanente Medical Care Program, northern C lifornia.

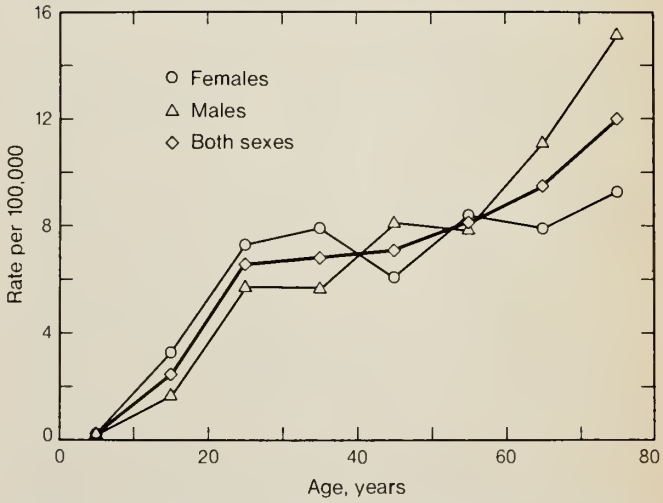

Figure 2.—The graph shows age-specific rates of first hospital admission in 1971-1982 for 868 persons with ulcerative colitis at the northern California Kaiser Permanente Medical Care Program.

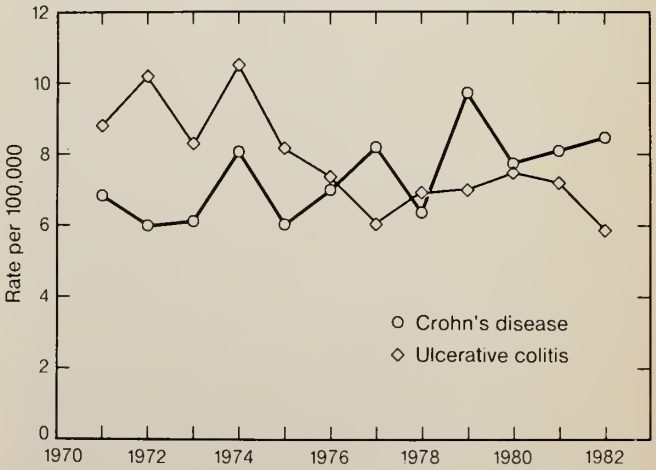

Figure 3.—The graph shows age-adjusted rates of persons admitted to hospital per year for Crohn's disease and ulcerative colitis at the northern California Kaiser Permanente Medical Care Program.

tended survey was the same. The proportion, however, that was admitted to hospital for ulcerative colitis—as opposed to being admitted for some other illness with ulcerative colitis as an associated diagnosis—in the over-70-years group was less. Hospital admissions were primarily due to ulcerative colitis for 86% of persons with a coded diagnosis of the disorder. But in the over-70-years group, only 50% were admitted for ulcerative colitis and only 20% were admitted for ulcerative proctitis. For Crohn's disease, 90% of hospital admissions were due to that disease.

There was no important difference in the frequency of misclassification by sex. Of 166 men, 130 (78%) were accurately classified as having inflammatory bowel disease; of 215 women, 156 (73%) had the disorder accurately classified.

The racial distribution of the random sample of patients is given in Table 3. This distribution is similar to the racial distribution of the northern California health plan membership as determined in an internal health plan survey in 1981.

Rates of Hospitalization of Validated Cases of Inflammatory Bowel Disease

If we use the proportion of definite and probable validated cases from our 20% random sample applied to the same proportion of the total membership population, we estimate that the mean annual rate of first hospital admission for the 1971-1982 period was 4.80 per 100,000 members for Crohn's disease, 4.19 per 100,000 for ulcerative colitis, and 0.16 per 100,000 for ulcerative proctitis. The male-to-female sex ratio was 0.7:1 for Crohn's disease and 1:1 for ulcerative proctitis, almost the same as for the total group. For Crohn's disease, the age at first diagnosis was highest in the age group 20 to 29 years and in a second mode was suggested in the 50- to 60-years group (Figure 4). Unlike the uncorrected hospital data for ulcerative colitis (Figure 2), there was a definite peak in the age group 20 to 29 years, but no mode was seen in the older age groups.

Outpatient Data

Of the 41 new cases of inflammatory bowel disease seen in the outpatient clinic at the Oakland facility between July 1980 and June 1981, there were identified 11 new cases of Crohn's disease, 11 of ulcerative colitis, and 6 of ulcerative proctitis. A total of 13 cases of self-limited colitis were discovered and excluded; a specific diagnosis, such as *Campylobacter,* was found in six patients, and no cause was evident in seven. Three more cases of Crohn's disease for patients who were directly admitted to hospital when seen initially were found by scrutinizing the hospital discharge data for that period. This yielded incidence rates of 10.9 per 100,000 for ulcerative proctocolitis and of 7.0 per 100,000 for Crohn's disease. The male:female ratio was 1.4:1 for ulcerative proctocolitis and 0.6:1 for Crohn's disease. The age-specific rates were remarkably similar for ulcerative colitis and for Crohn's disease, except in the age group 30 to 49 years, in which ulcerative colitis predominated (Table 4).

Of the 28 incident cases, only 6 (21%) were admitted to hospital for inflammatory bowel disease, either at the time of presentation or within the next 3½ years. Five of these six patients had Crohn's disease. Thus, 5 of 11 cases of Crohn's disease (45%) but only 1 of 17 cases of ulcerative colitis and ulcerative proctitis (6%) were admitted to hospital in that period.

Discussion

The limitations of hospital data for drawing inferences in epidemiologic studies are reasonably well known and have been discussed in the literature on inflammatory bowel disease.[14,15] Recognizing these limitations in the KPMCP hospital data, we wished to examine them, nevertheless, to assess their implications for our understanding of the epidemiology of the disease. We also wanted to compare them with outpatient incidence data in a subset of the same population.

Several properties of the hospital discharge data could induce misleading conclusions about inflammatory bowel

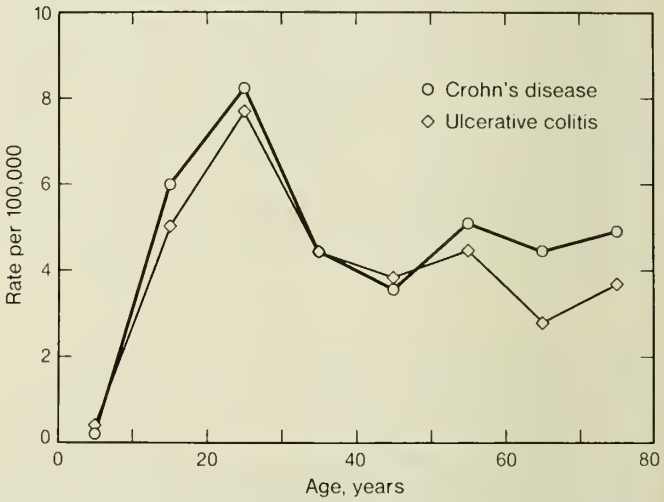

Figure 4.—The graph shows the estimated age-specific rates of first hospital admission in 1971-1982 for persons with inflammatory bowel disease based on validated diagnoses of Crohn's disease and ulcerative proctocolitis at the northern California Kaiser Permanente Medical Care Program.

TABLE 3.—*Racial Distribution of 285 Validated Cases Compared With General Membership of Health Plan*

Race	*Member Survey 1981, %*	*Crohn's Disease, No. (%)*	*Ulcerative Colitis, No. (%)*	*Ulcerative Proctitis, No. (%)*
White	81	127 (85)	112 (86)	5 (100)
Black	7	12 (8)	9 (7)	0
Asian	7	0	3 (2)	0
Hispanic	*	0	2 (1)	0
Other	5	1 (1)	0	0
Unknown	...	9 (6)	5 (4)	0
Total	100	149	131	5

*10% of respondents included in other racial groups were of Hispanic origin or descent.

TABLE 4.—*Incidence of Inflammatory Bowel Disease per 100,000 Members, 1980-1981, Oakland Facility*

Age Group at Diagnosis, years	*Ulcerative Proctocolitis, Rate (n)*	*Crohn's Disease Rate (n)*
0-9	0	0
10-29	9.1 (5)	9.1 (5)
30-49	19.0 (9)	6.3 (3)
50-69	7.7 (2)	7.7 (2)
70+	14.3 (1)	14.3 (1)
Mean (total)	10.9 (17)	7.0 (11)
Male:female ratio	10:7	4:7

disease in this population. We have attempted to quantify each of these factors.

• *Misclassification of other diseases*—codes that did not actually represent cases of inflammatory bowel disease. We found that even when we restricted ourselves to ICDA diagnostic codes that were supposed to be specific for the disease—563.0 and 563.1, eighth edition—only 84% could be confirmed. Almost half of the misclassifications were either infectious gastroenteritis or colitis, irritable bowel syndrome, or radiation enteritis.

• *Misclassification by form of inflammatory bowel disease*—codes for one type of inflammatory bowel disease identified cases coded with the other form of the disease. Misclassification between types of the disease was more likely for cases coded with ulcerative colitis (563.1) at 10% than for cases coded with Crohn's disease (563.0) at 2%.

Just considering these two types of misclassification, crude rates of first hospital admission were reduced by 12% for Crohn's disease and by 28% for ulcerative proctocolitis. These adjusted rates are our closest estimate of the incidence of first hospital admission and can be used for comparison with other studies.

• *Earlier diagnosis*—some cases are diagnosed before the first hospital admission for inflammatory bowel disease. We found that only about a third of these cases were first diagnosed in the same year as their first hospital admission.

• *Hospital admission with or for inflammatory bowel disease*—persons with the disease are admitted to hospital for other nonrelated diagnoses but their cases are still coded as inflammatory bowel disease at discharge. We found that most hospital admissions (85% to 90%) associated with a code for inflammatory bowel disease were for that disease and not for some other illness with inflammatory bowel disease being listed as a secondary diagnosis. By contrast, the high rate of hospital admission for ulcerative colitis for those older than 80 years did not represent the true incidence of the disease, since about half of these patients were admitted to hospital for another disease and ulcerative colitis was included as an associated diagnosis.

• *Outpatient cases*—not all patients with inflammatory bowel disease are treated in hospital. By comparing inpatient and outpatient data from Oakland in the July 1980 to June 1981 period, we found that only 21% were admitted to hospital during the next 3½ years. A longer follow-up should reveal more hospital admissions, but the rate of admission, especially for ulcerative colitis, is still low. The fact that most patients with inflammatory bowel disease are not admitted to hospital sharply limits the usefulness of hospital rates.[14,15] Hospital rates can grossly underestimate true incidence rates; the magnitude of this underestimation could differ in different areas of the world and even among different health care systems in the same locale according to the criteria used to admit these patients to hospital.

Thus, rates based on hospital admissions have little to recommend them; their primary virtue is that they are more readily available. In comparing our findings with those of other populations, we will distinguish between hospital rates and incidence rates, although both are population-based.

The corrected rates of first hospital admission in this northern California population are comparable to those on first hospital admission in the same time period from Baltimore, the only other population-based hospital data on inflammatory bowel disease in the United States.[3] Other comparisons, based on hospital data from Europe, generally show ulcerative colitis rates between 3 and 8 per 100,000[1,9,15,16] and Crohn's disease rates between 1 and 7 per 100,000.[1,10,15,16] Much of the variation in these rates could occur because of the population studied, the definition of inflammatory bowel disease, and the location and time period of the study, as well as the factors mentioned above.[1] For the actual incidence, which counts all new cases in a population, only figures from Olmsted County, Minnesota, are available in the United States.[2,3] In the period 1955 through 1964, ulcerative colitis rates were 8.7 per 100,000[2] compared with 10.9 per 100,000 in Oakland in the 1980-1981 one-year period. For Crohn's disease, rates were reported for 1965 through 1975 at 6.6 per 100,000[3] compared with 7.0 per 100,000 in Oakland. The incidence rate for Crohn's disease was substantially closer to the hospital admission rate in the KPMCP hospitals than that for ulcerative colitis. This implies that more persons are admitted to hospital for Crohn's disease than for ulcerative colitis, an impression supported by the fact that five of the six persons admitted to hospital in the Oakland group had Crohn's disease. Our rate for the incidence of ulcerative colitis is among the highest reported and is comparable to rates reported from community-based studies in northeastern Scotland[7] and the county of Copenhagen.[11]

For ulcerative colitis, men and women were equally affected, but there was a slight predominance of women with Crohn's disease. During the period 1977 through 1979 among whites in Baltimore, more male patients were admitted to hospital for ulcerative colitis and slightly more female patients were admitted for Crohn's disease[6]; in earlier surveys in the same population,[4] the ratios were reversed. In Olmsted County[2,3] and in European studies,[17,18] the sex ratio for both diseases is close to unity. Some have suggested that the rates of Crohn's disease may be higher among women during the early reproductive years because of the putative effect of oral contraceptives.[19] We conclude, however, that there is no important overall sexual difference in the occurrence of inflammatory bowel disease.

A bimodal age distribution for Crohn's disease follows the pattern seen in most previous studies in this and other countries.[1,5,6,11,20] On the other hand, the age-specific rates in Malmö, Sweden, show the early peak only in the age group 20 to 29 years.[21] The corrected hospital data do not suggest a bimodal pattern for ulcerative colitis, although when the rates of first hospital admission are examined next to age-specific rates produced by Garland and co-workers,[5] differences are not great. A bimodal age distribution for ulcerative colitis has been noted in European populations,[7,18,22] although there are again exceptions with only one mode.[18,22]

Time trends based on hospital records are also subject to biases introduced by the tendencies of physicians in different communities to admit their patients who have inflammatory bowel disease.[1] As diagnosis and treatment techniques improve, patients are more likely to be treated as outpatients and not need hospital care. Upward trends are less likely to be spurious for this reason, although the magnitude of the increase may be inhibited by such a bias. We found a distinct downward trend in hospital admissions per year for ulcerative proctocolitis. Rates fell from nine to ten hospital admissions per year in the early 1970s to six per year in 1982. This is similar to the rates in Baltimore between 1973 and 1977-1979[6] and in Stockholm in the 1970s[23] but not to those

in Copenhagen, where ulcerative colitis rates may be rising.[17] On the other hand, the rate of hospital admissions for Crohn's disease increased slightly from 6 to 7 per 100,000 to more than 8 per 100,000 in the same period. A substantial increase in the incidence of Crohn's disease has been noted in most populations,[24,25] although not all.[26] The relative frequency of Crohn's disease and ulcerative colitis also seems to have changed in our population in the past decade. This could be explained by changing diagnostic conventions that have recognized Crohn's disease as a colonic disease.[15,25] Of course, there might actually be an increasing incidence of Crohn's disease in northern California.

We did not find any notable racial differences in the rate of inflammatory bowel disease compared with the rate in the total health plan population, although others have stated that the disease is more common among whites than among blacks.[15] Data to support this contention are found in early studies from Baltimore[4]; from South Africa, where inflammatory bowel disease is rarely reported in blacks[27]; and from New Zealand, where it is rare among Maoris.[28] A more recent study from Baltimore[6] has shown much less of a difference in rates by race: for women, both Crohn's disease and ulcerative colitis were more common in blacks than in whites. Few studies have examined racial differences in a population where all persons have equal access to medical care, as they do in the KPMCP. These findings make it unlikely that racial differences are as important as environmental and medical care factors in explaining the differences in rates between blacks and whites reported from previous studies.[4,27,28] On the other hand, we had only three cases of ulcerative colitis and no cases of Crohn's disease among Asians despite the fact that 7% of our health plan members were of Asian descent.

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Clinical Medicine

Use of APACHE II Classification to Evaluate Outcome of Patients Receiving Hemodialysis in an Intensive Care Unit

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We retrospectively reviewed the medical records of all patients who were admitted to the medical and surgical intensive care units of a university center (N = 100) and its affiliated veterans' hospital (N = 46) between 1982 and 1986 to receive dialysis. The APACHE II severity-of-disease classification was used to identify the cases in which the prognosis was so poor that no long-term benefit would accrue from hemodialysis treatment. A "risk of death" was calculated for each patient. At a risk of death of 70% or greater, the system correctly predicted the demise of patients with 100% specificity regardless of what interventions were carried out. Sensitivity and predicted negative value were low in all cases, however, indicating a poor predictability of those who will survive. Withholding the average of 6 dialysis treatments that this group of patients received would probably have reduced patient suffering during a lingering terminal illness and led to a savings of about $4,500 per patient.

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Changes in American medical practice in recent years have been remarkable. Each technologic advance in diagnostic or treatment capability, however, carries a cost that is also impressive. With growing competition for available health care dollars, physicians must justify expensive procedures, particularly in critically ill patients with a poor prognosis.

Toward that goal, Knaus and associates developed a severity-of-disease classification system, the Acute Physiology and Chronic Health Evaluation (APACHE), that showed strong, stable relationships between the severity of illness and the subsequent probability of death from various diseases commonly treated in intensive care units (ICUs).[1-3] The system was later revised and simplified into APACHE II, which used fewer but readily available measurements; the accuracy of the original system was maintained.[1-3]

In this study we used the APACHE II system to evaluate mortality in patients who received hemodialysis in an ICU. The purpose of our investigation was to develop a method of identifying those cases in which dialysis was unlikely to provide benefit. From an ethical perspective, a prognostic classification for excluding a patient from dialysis must approach infallibility. We found the APACHE II classification a reasonable way to discern which patients in an ICU had such a high probability of dying that hemodialysis did not improve survival. As an addendum, the cost-effectiveness of overall ICU care could also be improved.

Patients and Methods

APACHE II Classification

The APACHE II classification is largely based on 12 physiologic variables (called the Acute Physiology Score [APS]) that are weighted according to their deviation from the normal range as a measurement of the acute physiologic derangement of a patient. A final APACHE II score is calculated from the APS combined with a weighted score for the patient's age and a score based on the severity of the underlying chronic illness at the time of admission to the ICU. A prior use of the APACHE II system showed that the "risk of death" calculation was influenced by both the APACHE II score and by the disease process causing the ICU admission. Weighted scores for various diseases were empirically derived. A logistic multiple regression equation was developed using both the APACHE II score and the diagnostic category weight for predicting the risk of death in individual patients. This method was verified in an extensive multicenter study involving 13 hospitals and more than 5,800 patients.[2] The following example shows the use of this method:

Example. A 64-year-old woman with a history of diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal insufficiency was admitted to the intensive care unit for treatment of respiratory failure from extensive pneumonia. None of her chronic organ disease was sufficient to warrant Chronic Health Points.[2] Her admitting APS of 18, combined with an age point value of 3, gives a total APACHE II score of 21. Her estimated risk of death is calculated by the following equation:

$$\ln(R/1-R) = -3.517 + (\text{APACHE II score} \times 0.146) + 0.603\ (\text{only if an emergency operation was done}) + (\text{diagnostic category weight})$$

where R is the risk of hospital death. In this patient,

$$\begin{aligned} \ln(R/1-R) &= -3.517 + (21 \times 0.146) + 0 + 0 \\ &= -3.517 + 3.066 \\ &= -0.451 \\ R/1-R &= 0.639 \\ R &= 0.389 \text{ or } 38.9\%. \end{aligned}$$

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ABBREVIATIONS USED IN TEXT

APACHE = Acute Physiology and Chronic Health Evaluation
APS = Acute Physiology Score
ICU = intensive care unit

Study Patients

The medical records of all patients admitted to the ICU who received dialysis at the Jerry L. Pettis Memorial Veterans Administration Medical Center and the Loma Linda (California) University Medical Center between 1982 and 1986 were retrospectively reviewed. Following the technique of Chang and co-workers who evaluated the benefit from total parenteral nutrition,[4] each patient's APACHE II score was determined from the worst values over the first 24 hours of admission to the ICU and the 24 hours before the time hemodialysis was instituted. It was initially thought that one of these scores might be more predictive of death.

A total of 196 patients were identified for the study from dialysis records, but the records of 31 were not evaluated: 29 were never actually admitted to an ICU and 2 were transferred from an ICU before dialysis. Of the remaining 165 patients, 19 could not be evaluated as inadequate medical records militated against accurately determining the APACHE II scores. The results of this study were based on the records of the remaining 146 patients.

The criteria for hemodialysis did not differ in patients included in this study from those customarily used outside an ICU setting and included severe hyperkalemia, metabolic acidosis, progressive azotemia, or fluid overload. Fluid overload appeared more frequently in these patients because of attempts to administer adequate nutrition by parenteral or liquid enteral feedings.

Analysis of Data

The APACHE II data for each patient were entered into an IBM-XT computer and the risk of death calculated. Values for sensitivity, specificity, positive predictive value, and negative predictive value were calculated by standard formulas.[4] Confidence intervals for various percentages were calculated by the following techniques: For percentages between 85% and 100%, calculations were made by Poisson approximations of the binomial distribution. For percentages of less than 85%, calculations were made from a normal approximation of the binomial distribution. When a zero numerator was present (risk of death 70% or greater), an approximation based on the calculation of Hanley and Lippman-Hand was used.[5]

Results

The characteristics of the study patient population are shown in Table 1. The predicted and actual outcomes of patients at varying risk levels of death are recorded in Tables 2 and 3. Levels of the risk of death calculated from the APACHE II scores on the day of admission to the ICU are shown in Table 2, and Table 3 contains calculations based on the date of the initial hemodialysis treatment. The specificity in predicting death increased with the increasing level of risk, reaching 100% for all patients with a 70% or greater predicted risk of death. As specificity increased, however, sensitivity diminished. This pattern was similar whether using APACHE II scores from the ICU admission date or from the date that dialysis was instituted. Both identified a risk level of 70% or greater as showing 100% specificity for death. The 23 patients predicted to die at a 70% risk level using the ICU admission date did die, as did the 35 predicted from the data on the date dialysis was started. The sensitivity at this level was 25.8% and 39.3%, respectively.

In an attempt to increase the overall sensitivity for predicting hospital mortality, a combination of risk levels from information gathered on both the admitting ICU date and the dialysis date was used. The following combinations were evaluated: 70% or greater on the admission date or less than 70% on the admission date with 40% or greater on the initial dialysis date, 70% or greater on the admission date or less than 70% on the admission date with 50% or greater on the dialysis date, and 70% or greater on the admission date or less than 70% on the admission date with 60% or greater on the dialysis date. Although the sensitivities were better—75.3%, 59.6%, and 49.3%, respectively—only the last combination approached 100% specificity.

The possibility that the subgroup of patients already receiving continuous hemodialysis might have different outcomes was also evaluated (Table 4). At a 70% risk level we again showed 100% specificity, but because this subgroup was small, the 95% confidence limits were large and definitive conclusions cannot be made with these data.

Discussion

The APACHE system was developed to enable groups of patients receiving different types of therapies to be compared. The originators emphasized that it was not developed to aid decision making about treating individual patients as proposed in this study. Nonetheless, as Chang and co-workers have previously reported and as shown in this report, the accuracy of predicting death is remarkable.[4] As noted by all who use this classification system, however, it is better at predicting those who will die than those who will live (low sensitivity and low negative predictive value).

Admittedly, by the very nature of our basic objective, a specific subset of the general ICU patient population was selected who may have a higher risk of death because of renal failure. This probably explains why 100% specificity was

TABLE 1.—*Distribution of Patients (N=146) by Various Characteristics*

Characteristic	*Patients, Number*
Male	116
Female	30
Mean age, years (range)	61 (22-83)
Hospital location	
Loma Linda University Medical Center	100
Loma Linda Veterans' Hospital	46
Type of intensive care unit	
Coronary care unit	19
Medical	21
General surgical	18
Cardiothoracic surgical	15
Combined medical and surgical	59
Pulmonary	13
Neurosurgical	1
Clinical condition	
Receiving continuous hemodialysis	24
Postoperative	58
Severe trauma	1
After renal transplant	14
Miscellaneous conditions	49

TABLE 2.—*Actual and Predicted Outcome at Different Risk Levels of Death Using Calculations at ICU Admission Date for Patients Receiving Hemodialysis**

Level of Risk		Patients Predicted: To Live (Number)	To Die (Number)	Total (Number)	Sensitivity, %†	Specificity, %†	Predictive Positive Value, %	Predictive Negative Value, %
40%					59.5 (28.2, 90.8)	84.2 (76.6, 91.6)	85.5	57.1
	Actually alive . . .	48	9	57				
	Actually dead . . .	36	53	89				
	Total	84	62	146				
50%					47.2 (36.8, 57.6)	93.0 (82.0, 98.1)	91.3	53.0
	Actually alive . . .	53	4	57				
	Actually dead . . .	47	42	89				
	Total	100	46	146				
60%					33.7 (23.9, 43.5)	96.5 (87.3, 99.6)	93.8	48.2
	Actually alive . . .	55	2	57				
	Actually dead . . .	59	30	89				
	Total	114	32	146				
70%					25.8 (16.7, 34.9)	100 (94.7, 100)	100	46.3
	Actually alive . . .	57	0	57				
	Actually dead . . .	66	23	89				
	Total	123	23	146				
80%					11.2 (4.6, 17.8)	100 (94.7, 100)	100	42.0
	Actually alive . . .	57	0	57				
	Actually dead . . .	79	10	89				
	Total	136	10	146				

ICU=intensive care unit

*Patients with a risk of death greater or equal to the listed level were predicted to die.
†Values in parentheses represent the 95% confidence interval for each mean percentage.

TABLE 3.—*Actual and Predicted Outcome at Different Levels of Risk Using Calculations on the Date of Initiation of Dialysis**

Level of Risk		Patients Predicted: To Live (Number)	To Die (Number)	Total (Number)	Sensitivity, %†	Specificity, %†	Predictive Positive Value, %	Predictive Negative Value, %
40%					71.9 (62.6, 81.2)	77.2 (68.5, 85.9)	83.1	63.8
	Actually alive . . .	44	13	57				
	Actually dead . . .	25	64	89				
	Total	69	77	146				
50%					53.1 (42.7, 63.5)	86.0 (72.4, 93.9)	86.7	57.0
	Actually alive . . .	49	8	57				
	Actually dead . . .	37	52	89				
	Total	86	60	146				
60%					48.3 (37.9, 58.7)	93.0 (82.0, 98.1)	91.5	53.5
	Actually alive . . .	53	4	57				
	Actually dead . . .	46	43	89				
	Total	99	47	146				
70%					39.3 (29.2, 49.4)	100 (94.7, 100)	100	51.4
	Actually alive . . .	57	0	57				
	Actually dead . . .	54	35	89				
	Total	111	35	146				
80%					15.7 (8.1, 23.3)	100 (94.7, 100)	100	43.2
	Actually alive . . .	57	0	57				
	Actually dead . . .	75	14	89				
	Total	132	14	146				

*Patients with a risk of death greater or equal to the listed level were predicted to die.
†Values in parentheses represent the 95% confidence interval for each mean percentage.

TABLE 4.—*Actual and Predicted Outcome at Different Levels of Risk for Those Patients Already Receiving Continuous Dialysis**

Level of Risk		Patients Predicted: To Live (Number)	Patients Predicted: To Die (Number)	Patients Predicted: Total (Number)	Sensitivity, %†	Specificity, %†	Predictive Positive Value, %	Predictive Negative Value, %
40%					66.6 (28.9, 100)	94.4 (69.1, 99.9)	80.0	89.5
	Actually alive . . .	17	1	18				
	Actually dead . . .	2	4	6				
	Total	19	5	24				
50%					66.6 (28.9, 100)	94.4 (69.1, 99.9)	80.0	89.5
	Actually alive . . .	17	1	18				
	Actually dead . . .	2	4	6				
	Total	19	5	24				
60%					66.6 (28.9, 100)	94.4 (69.1, 99.9)	80.0	89.5
	Actually alive . . .	17	1	18				
	Actually dead . . .	2	4	6				
	Total	19	5	24				
70%					16.6 (0.0, 46.4)	100 (83.3, 100)	100	78.3
	Actually alive . . .	18	0	18				
	Actually dead . . .	5	1	6				
	Total	23	1	24				

*Patients with a risk of death greater or equal to the listed level were predicted to die.
†Values in parentheses represent the 95% confidence interval for each mean percentage.

seen at a lower level than that in the previous reports.[3,4] Therefore, the absolute accuracy of the APACHE II system as previously determined may not be directly related to our particular patient subset. Nevertheless, we feel these results have revalidated the usefulness of the APACHE II system as a highly specific predictor of mortality in an ICU even in this subset of patients. At a calculated risk level of 70% or greater, death was predicted correctly in all cases. Like the study of Chang and colleagues who used the APACHE II classification to identify ICU cases for which total parenteral nutrition would not provide a benefit, this study showed an improvement in sensitivity in predicting death by using combinations of risk levels on ICU admission and the initial dialysis date. As noted, we were never able to achieve the 100% specificity that was achieved using data from the admitting or dialysis date alone. The usefulness of this type of evaluation depends on its near infallibility; therefore, using combinations of risk levels did not add to its usefulness.

Using an average cost of $750 per hemodialysis treatment, withholding one treatment from the 23 patients correctly predicted to die (Table 2) would have saved about $17,250. Because patients received 1 to 20 or more dialysis treatments, it is obvious that a substantial cost is involved. With 6 as the average number of hemodialysis sessions per patient, about $103,500 would have been saved.

The withholding of therapy from terminally ill patients has received considerable discussion in both the medical and lay literature in recent years. Well-publicized cases such as those of Karen Quinlan, Elizabeth Bouvia, Clarence Herbert, and others have led to an outpouring of both legal and ethical comments on the subject.[6,7] Wanzer and associates attempted to outline a reasonable approach to the level of care that should be given to a hopelessly ill patient.[8] Yet, even in their proposal, no standard of care can be applied to all situations.

The desires of a patient when known, the desires of the family when the patient's wishes are unknown, and the varied experiences of different clinicians must all be considered before making decisions. Yet, as experience grows with a probabilistic system such as APACHE II, physicians can have a strong, objective indicator of patients for whom various forms of acute intervention may serve no useful purpose.[9] In such cases, dialysis becomes extraordinary treatment because it is medically impossible or futile, it provides no benefits in terms of prolonging life or alleviating suffering, or the resulting burdens on the patients are excessive in relation to the benefits gained.[10] It is hoped that this will help physicians practice more humane and, in the end, more cost-effective critical care medicine. A caveat from a *Lancet* editorial, however, should be remembered: "probability is only one factor to be taken into account when making a clinical decision. Statistics should be used as the drunken man uses the lamppost—for support rather than illumination."[11]

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Long-term Effects of Exposure to Diethylstilbestrol

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In 1985 nearly 1,700 persons who had exposure to diethylstilbestrol (DES)—520 mothers, 1,079 daughters, and 94 sons—responded to a mailed questionnaire about their general health status. Results were compared with responses to the 1985 National Health Interview Survey and other population-based studies. As with research findings in animals, conditions that suggest possibly impaired immune function—that is, respiratory tract infections, asthma, arthritis, and lupus—were reported more frequently among the persons with DES exposure. Conditions that may involve altered endocrine function were also more frequent among such persons. Given the biased sample, findings from this preliminary survey are seen as guidelines to areas meriting more rigorous research.

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Between 1940 and 1972, a synthetic nonsteroidal estrogen, diethylstilbestrol (DES), was prescribed to millions of pregnant women throughout the United States and other countries in an attempt to treat or prevent pregnancy problems.[1] The failure of DES to improve pregnancy outcome was shown in the early 1950s[2]; the prescribing of DES during pregnancy, however, continued as a standard practice in the US, with about 3 to 6 million women and their offspring having exposure to the synthetic estrogen (an estimate based on figures from the Boston Collaborative Drug Surveillance program and the National Cancer Institute's Request for Proposal to establish the National Cooperative Diethylstilbestrol-Adenosis Project [DESAD], December 1, 1973).[3] Twenty years later, the first major unintended result of this therapy became apparent when a rare vaginal tumor in young women—clear cell adenocarcinoma—was linked to prenatal DES exposure.[4] At that time, the Food and Drug Administration withdrew approval for the use of DES as a miscarriage preventive.

The identification of the extremely rare vaginal and then cervical cancer marked the first known instance of human transplacental carcinogenesis. While the clear cell cancer risk is low for daughters with exposure to DES—about 1 in 1,000 by her mid-30s[5]—a large, well-controlled study has shown a twofold increase in the risk for cervical and vaginal dysplasia and carcinoma in situ among these women.[6]

Research on humans has concentrated on genital tract pathologic disorders. Among daughters with exposure to DES, non-neoplastic changes and reproductive problems are more common than cancer.[7-12] Less research has focused on sons with the exposure, and results have been more contradictory. Studies, however, have shown increased rates of urogenital tract abnormalities—including epididymal cysts and undescended testes—in men with prenatal exposure to DES.[11,13]

Questions remain about additional health effects associated with DES exposure, especially among those receiving exposure in utero. Clearly, prenatal exposure resulted in more than a single defect, including conditions that have a higher background rate in the general population than did the originally identified vaginal tumor. With the great majority of this cohort still younger than 40 years, the age of increased cancer risk for various sites has yet to be reached.

Research using experimental animal models and concerned primarily with elucidating mechanisms of DES effects raises questions regarding future health consequences in the human population. While these studies cannot directly predict human outcomes, they suggest possible areas of inquiry. A critical question requiring study in humans is whether prenatal DES exposure results in long-term immunologic effects. In mice, perinatal DES exposure in certain genetic strains results in impaired immune system functioning.[14,15] Corresponding immunologic consequences in humans could be important not only for the development of cancer but for a range of other health conditions. Other areas of concern arising from experimental studies in animals include the breast and ovary in daughters,[16-20] the prostate and testes in sons,[21] and endocrine alterations in both women and men with prenatal exposure to DES.[16,22,23] Concerns about possible health effects beyond genital tract disorders prompted a survey of the health status of persons with known exposure to DES. The aim of this preliminary survey was to provide guidelines regarding areas meriting more rigorous research.

Methods

In 1985 a questionnaire was mailed to 2,000 persons who subscribe to a quarterly newsletter published by DES Action, USA. This voluntary, nonprofit organization provides information and support to those with DES exposure and their health care providers. The questionnaire was also sent to 3,000 persons who had contacted the organization for infor-

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ABBREVIATIONS USED IN TEXT

DES = diethylstilbestrol
MCA = 3-methylcholanthrene

mation such as physician referrals but who had not subscribed to the newsletter.

About 1,700 persons responded—520 mothers, 1,079 daughters, and 94 sons. Between 80% and 90% reported definite exposure. Approximately 40% of the mothers and daughters and 20% of the sons reported that they had received validation of their exposure—more than 50% of those requesting such information. Exposures were reported between 1941 and the late 1970s, the latter in Mexico.

Where possible, the rates of conditions reported were compared with those reported in the 1985 National Health Interview Survey[24] or in population-based studies.[25,26]

Results

Many conditions already known or suspected to be associated with DES exposure were reported more frequently than expected. For example, 1.3% of the daughters reported clear cell adenocarcinoma of the vagina or cervix compared with less than 0.1% in published reports.[5] This disparity is presumably due to self-selection of the sample. That is, daughters who have experienced clear cell adenocarcinoma would be more likely to subscribe to the DES Action newsletter and therefore be overrepresented. Such a bias is less likely to occur in those contacting the organization for information only than in those subscribing to the newsletter because they may be less certain of exposure or have experienced less frequent or severe known DES effects. Analyses comparing the rates of DES-associated conditions among these two groups (not shown) indicate that the rates were higher among those subscribing to the newsletter, while rates among those contacting DES Action, USA for information only were similar to those in published reports based on unbiased samples of persons with DES exposure—that is, those identified by reviewing records.

Conditions not known to be associated with DES exposure were also reported more frequently than expected. As can be seen in Table 1, the number of reported colds, flu, and respiratory tract conditions during the past year in daughters and sons was three times as high as the number reported for comparable age and sex groups in the 1985 National Health Interview Survey.[24] Among mothers receiving DES, the number was about twice as high. Both surveys are based on self-reported health conditions.

TABLE 1.—*Respiratory Tract Conditions Among Adults From the Diethylstilbestrol (DES) Survey (This Study) and the National Health Interview Survey (1985)**

DES Survey			*National Health Interview Survey*		
Person	*Age, years*	*Rate†*	*Person*	*Age, years*	*Rate†*
Daughters, N=1,079	14-44	255	Women	18-44	96
Sons, N=94	14-44	207	Men	18-44	69
Mothers, N=520	27-77	130	Women	45+	59
				All ages	94

*From National Center for Health Statistics.[24]
†Number of respiratory tract conditions per 100 persons per year.

TABLE 2.—*Prevalence Rates (%) of Selected Conditions Among Adults With Diethylstilbestrol (DES) Exposure*

	DES-Exposed (This Study)			*Comparison**		
Condition	*Person (N=1,693)*	*%*	*No.†*	*Group, age*	*%*	*P Value‡*
Asthma						
	Daughters	9.6	104	Women, <45 years	4.2	≤.001
	Sons	14.9	14	Men, <45 years	3.6	≤.001
	Mothers	8.3	43	Women, 45-64 years	2.9	≤.001
Arthritis						
	Daughters	7.8	84	Women, <45 years	4.4	≤.001
	Sons	8.5	8	Men, <45 years	2.2	≤.001
	Mothers	41.9	218	Women, 45-64 years	32.5	≤.001
Lupus erythematosus						
	Daughters	0.7	8	Women, all ages	0.002	
	Sons	0.0	0	Men, all ages	0.0002	
	Mothers	1.0	5	Women, all ages	0.002	
Diabetes mellitus						
	Daughters	1.0	11	Women, <45 years	0.7	≤.05
	Sons	3.2	3	Men, <45 years	0.6	≤.01
	Mothers	5.6	29	Women, 45-64 years	5.1	NS
Prostate problems						
	Sons	14.9	14	Men, <45 years	0.3	≤.001

NS=not significant

*All data are from the National Center for Health Statistics,[24] except the data for lupus erythematosus, which are from Isselbacher et al.[25]
†Daughters numbered 1,079, sons numbered 94, and mothers numbered 520.
‡Based on χ^2 statistic.

Other conditions reported in apparently high numbers when compared with population-based data[24,25] are presented in Table 2. Prevalence rates were higher among those with exposure to DES for asthma, arthritis, lupus, diabetes mellitus, and prostate problems. Virtually all of these differences were statistically significant (based on χ^2 statistics). Arthritis reported by daughters and sons generally occurred early: the median age for the beginning of arthritis was 24 years for daughters and 17 years for sons. In addition, 38 daughters (3.5%) reported high prolactin levels, and 7 (0.6%) reported pituitary tumors. The annual incidence rate of pituitary tumors in women 15 to 44 years old was reported to be 0.007 between 1970 and 1977 in Minnesota.[26]

While it was expected that conditions known to be associated with DES exposure would be overreported, conditions with no known association were considered unlikely to be overreported to the same degree. Rates of the conditions presented in Table 2 were compared for respondents who had subscribed to the DES Action newsletter and those who had contacted the organization for information only, on the theory that the latter group should exhibit less reporting bias. Unlike the rates of conditions known to be associated with DES exposure, there was generally no difference in the rates of these other disorders in the two groups. In addition, rates of asthma, arthritis, and respiratory tract problems were calculated for DES daughters who were both sure of their exposure and reported DES-associated conditions—adenosis, cervical anomalies such as hoods or ridges, or clear cell adenocarcinoma of the vagina or cervix. These women are more likely to have had early or higher dose exposures. Rates were comparable to those reported for DES daughters in Tables 1 and 2 and still significantly higher than those for similarly aged women from the National Health Interview Survey. This was the case whether or not the 12 daughters with cancer were included in the analyses.

Discussion

The present survey represents a preliminary look at possible health effects of prenatal exposure to DES in humans beyond those already known. As such, it should be considered as a guide to areas needing further investigation in less biased samples. The findings, however, are consistent with those of experimental studies in animals and indicate a need for follow-up in the human cohort. Of particular note are conditions that suggest impaired immune function, such as infectious illness, allergic and autoimmune conditions, and malignant tumors. Studies of certain genetic strains of mice with exposure to DES during the critical neonatal period of immune system ontogeny—analogous to the first trimester of human pregnancy—show persistent, lifelong immunosuppression. The main DES effect is a reduced number of T-helper cells, important for the induction and regulation of many immune responses.[14,15] B-cell response is impaired in assays requiring T-cell mediation but is normal if corrected for T-helper numbers.[14] Experiments with varying combinations of B and T cells in vitro show that the defect is in T-cell number but not function.[14]

Mice with neonatal exposure also have a reduced number of natural killer cells thought to recognize and kill certain tumor cells.[14,15] Following injection with a classic carcinogen (3-methylcholanthrene [MCA]), DES-exposed mice show a reduced ability to resist tumors; MCA-induced sarcomas appear in greater numbers and at a faster rate.

Our findings regarding asthma, arthritis, and lupus are also consistent with those of a small study of human peripheral blood lymphocytes suggesting a hyperreactive immune response in women with in utero exposure to DES.[27] Another small study of the daughters suggested possible functional alterations of natural killer cells.[28] Even more suggestive, our findings are consistent with those of a recent preliminary report from the largest ongoing follow-up of DES daughters, the federally funded Diethylstilbestrol Adenosis Project.[29] This report indicates about a twofold increase in autoimmune conditions in women with prenatal exposure compared with controls.[29] One small study of daughters who had had DES-associated cancer or reproductive problems showed no consistent increase in the rates of infectious disease but a suggestive increase in the rates of autoimmune disease compared with controls.[30]

Evaluating immunologic consequences in women and men with DES exposure will be complicated by possible genetic contributions and by varying dosage and timing of the prenatal exposure. Furthermore, health consequences might become detectable only as the population ages, when the immune system generally declines in competence.

Possible pathologic disorders of the prostate, as noted in our survey, were also noted in experimental models of DES effects in rodents.[21] In preliminary studies of mice with neonatal DES exposure, evidence of cytologic malignancy in the area of the prostate appeared only in the experimentally treated animals.[31] Recent experiments in which human fetal prostate tissue was grafted into DES-treated and untreated athymic nude mice and then allowed to continue growing revealed ductal dilation and persistent distortion of ductal architecture; these conditions could contribute to early or increased development of prostatic neoplasms (S. Mee, G.R. Cunha, C.V. Yonemura, et al, "The Effects of Diethylstilbestrol on Human Prostate Development," unpublished data, 1987).

Further inquiry should also focus on a possible increased prevalence of elevated prolactin levels among DES daughters. Substantial endocrine alterations occur in rodents; more specifically, experimental studies show that perinatal DES exposure results in a disruption of hypothalamic-pituitary feedback systems, including the regulation and production of prolactin.[16,22,23] While endocrine effects of a similar magnitude are not apparent within the human cohort, there could be an increase of more subtle functional alterations in daughters or sons (or both) with exposure to DES. Although difficult to measure, abnormal endocrine function could be contributing to a diminished reproductive capacity in ways beyond the more apparent and well-documented structural anomalies. Two small studies of plasma hormones in the daughters suggest abnormalities that may reflect a disturbance of hypothalamic-pituitary-ovarian function.[32,33] An additional study suggests that hyperprolactinemia may be a significant factor in infertility in daughters with DES exposure.[34]

Comprehensive follow-up of DES-exposed daughters and sons is required to answer questions about the long-term consequences of prenatal exposure. As the cohort ages and reaches new "milestones" of increased health risks, such follow-up can contribute to a more adequate assessment of this population's risks and to the early detection of various health conditions that may be affected by prenatal DES exposure and be responsive to treatment. In addition, an increased

knowledge of the health consequences associated with DES exposure addresses a broader scientific need to examine fully the results of this reproductive exposure. Women and men with in utero exposure to DES constitute a unique, identified cohort from which much can be learned about the hormonal effects on both normal and abnormal human development. This cohort can provide a greater understanding of developmental biology, sex differentiation, and pathologic processes in humans. Beyond the basic knowledge to be gained are implications for therapeutic substances in use currently or considered for the future.

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Medical Progress

Obesity
Part II—Treatment

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Conventional diets and increased exercise are the cornerstones of traditional therapy for obesity, but available data suggest that the most important component of any program is the associated behavior modification through which new ways of dealing with old problems can be learned and continually applied. This combined with very-low-calorie diets—less than 800 kcal per day—are in wide use, mostly under medical supervision. The currently available appetite-suppressing drugs are of limited efficacy, but many new ones are under active development and hold promise for the future. The most effective surgical intervention appears to be the gastric bypass operation, but this should be reserved for those who are at high risk from their obesity.

(Bray GA, Gray DS: Obesity. Part II—Treatment. West J Med 1988 Nov; 149:555-571)

Treating persons with weight problems has many similarities to treating those with other chronic illnesses. For example, hypertension can be effectively treated by current medications, yet the side effects and the need to treat those who may have no symptoms from their hypertension lead to high levels of therapeutic failure, including an unwillingness of hypertensive persons to seek medical help, an unwillingness to maintain treatment once it is prescribed, and terminating treatment because of some of the side effects of medications.

The treatment of overweight, like that of most chronic illnesses and addictive disorders, is palliative, not curative. That is, most treatment regimens for obesity, when completed, do not produce a permanent remission. A simple example is a case of appendicitis, where the patient is cured by surgical removal of the diseased appendix. Comparable results with the treatment of overweight are rare. One example would be an effective therapy for Cushing's disease where the primary presenting symptom was obesity. For most cases, we are seeking the alleviation of symptoms associated with obesity, not a cure.

Recidivism is a third reality of the treatment of obesity. Of those who lose weight on any treatment program, a significant percentage will fail to maintain this weight loss.[1] Differentiating those persons who will be successful in losing weight from those who will succeed less well is at best an inexact procedure. Some suggested indicators for determining those who are likely to succeed include the initial one-week weight loss, the frequency and regularity of attendance at a weight loss program, and the belief that a person can control his or her own weight. Additional insight is needed before we will be able to distinguish at the beginning of treatment those who will succeed from those who will not.

The fourth reality of treating obesity is its cost. Each year, more than $10 billion is spent on efforts to control weight gain or induce weight loss. The distribution of these costs into several categories is shown in Figure 1, where it can be noted that more than 50% of the expenditure is for diet foods, with the remainder distributed into several other categories.

Evaluating the Risk Associated With Obesity

Because all treatments entail some risk, the first essential in deciding whether treatment is appropriate and what that treatment should be is assessing the risk associated with adiposity. Two independent variables can be used for assessment. The first is the risk associated with total body fatness. Underweight persons have an increased risk for respiratory disease, tuberculosis, digestive disease, and some cancers. For overweight persons, on the other hand, cardiovascular disease, gallbladder disease, high blood pressure, and diabetes are the primary risks.[3] The pathogenesis of obesity was discussed in detail in part I.* Body weights associated with a body mass index (BMI) of 20 to 25 kg per m^2 have little or no increased risk. When the body mass index is below 20 kg per m^2 or above 27 kg per m^2, the risk increases curvilinearly. Those with a BMI of 25 to 30 kg per m^2 have low risk; those with a BMI between 30 and 35 kg per m^2 have moderate risk; a BMI between 35 and 40 kg per m^2 indicates high risk, and those with a BMI above 40 kg per m^2 have very high risk from their obesity.

A second component of risk related to body fat is the distribution of that fat (detailed in part I). The higher the proportion of abdominal or truncal fat, the greater the risk. The algorithm in Figure 2 provides a way of including both total body fat, as estimated from the BMI, and the distribution of body fat in making decisions about the relative risk from obesity. The ratio of the circumference of the abdomen or waist to that at the hips or gluteal region is defined as the abdominal-gluteal ratio or waist-hip ratio.

*Bray GA, Gray DS: "Obesity. Part I—Pathogenesis," *West J Med* 1988 Oct; 149:429-441.

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ABBREVIATIONS USED IN TEXT

BMI = body mass index
HDL = high-density lipoprotein
LDL = low-density lipoprotein
RDA = *Recommended Dietary Allowances*
TOPS = Take Off Pounds Sensibly

At any given level of body mass index, the risk to health is increased with a higher abdominal-gluteal or waist-hip ratio. Other factors that increase risk from obesity include the presence of medical problems such as diabetes mellitus, hypertension, or hyperlipidemia, age younger than 40 years, and male sex.[3]

Assessing Risk-Benefit of Treatment

The therapies for obesity can be divided into groups based on their relative risk (Figure 3). They can be further divided by whether they influence the nutrient intake or energy loss. In a quantitative sense, treatments that reduce energy intake have a greater potential for substantial weight loss than those that attempt to increase energy expenditure.

Because all of our nutrient energy comes from food, we can reduce nutrient intake to zero (starvation). Energy expenditure, on the other hand, has a minimum level associated with the energy required to maintain body temperature, to repair tissues, and to maintain function of the heart and other organs. Thus, simply staying in bed and spending no time in physical activity reduces energy expenditure to approximately 0.8 kcal per minute (1,150 kcal per day) for a normal adult. High levels of physical activity can increase this by not much more than twofold to threefold over 24 hours. Thus, for an initial weight loss, decreasing food intake has the most to recommend it, while changes in energy expenditure through physical activity appear to have a particular attractiveness in efforts at long-term maintenance of changed body weight and composition.

Diet

Basic Considerations

Before considering specific diets, there are a number of important general points to make about all diets. First, calories do count. There is little question that reducing caloric intake below expenditure is associated with changes in body composition. This phenomenon has been shown repeatedly over the past 100 years. The careful studies of many investigators have found that when caloric intake is reduced below expenditure, there is a predictable rate of weight loss. During World War II, Keys and colleagues showed a clear-cut, predictable reduction in body weight and body fat stores when the caloric intake of healthy young men was reduced to 1,650 kcal per day.[4] Kinsell and co-workers showed that the rate of weight loss of obese patients admitted to a metabolic ward and fed a fixed caloric intake was constant and predictable.[5] Moreover, this rate of weight loss is largely independent of the dietary composition despite wide variations in protein, carbohydrate, and total fat intake.[4,6]

Predicting weight loss for an individual patient can be more difficult. In a study by Garrow, the weight loss of women treated for three weeks on a metabolic ward with a diet of 800 kcal (3.5 megajoules) per day varied from 1 to more than 10 kg.[6] The rate of weight loss could be predicted from the metabolic expenditure of these women. Body weight in turn was the major predictor of metabolic expenditure. In general, the heavier the patient, the faster he or she will lose weight. Moreover, no adult patient who has been studied in a metabolic chamber has needed fewer than 1,200 kcal per day for maintaining weight.

The proportion of carbohydrate in the diet is a second important determinant of short-term weight loss. Restricting the carbohydrate in the diet leads to a sodium diuresis and a loss of intracellular and extracellular fluids with resulting weight loss.[7] Alternatively, substituting carbohydrate in a greatly restricted diet will lead to sodium retention and may be associated with transient gains in body weight.

The relationship of energy requirements to body weight can be estimated from several studies. The energy requirement for each extra kilogram of body weight increases approximately 22 kcal, which is the slope of the line relating 24-hour energy expenditure to body weight. Thus, a person who weighs 10 kg more than another will require, on average, about 220 kcal per day more to maintain that extra weight. If caloric intake is restricted to the same level as part of a treatment program, the person with the higher body weight will withdraw more energy from fat stores and lose weight more rapidly. Within any weight group, however, there is a variability of energy expenditure. The expected or calculated energy expenditure for a woman weighing 100 kg (220 lb) is 2,650 kcal per day. A variability of ± 20% could give an expenditure as high as 3,180 kcal per day or as low as 2,120 kcal per day. Energy requirements are modified by age and sex. On any given diet men will lose a greater amount of weight than women of similar height and weight because they have more lean body mass and thus a higher energy expenditure. Older persons of either sex at comparable weights will have lower metabolic expenditures because the metabolic rate declines by 2% per decade of life.

Projecting metabolic ward studies to an outpatient setting

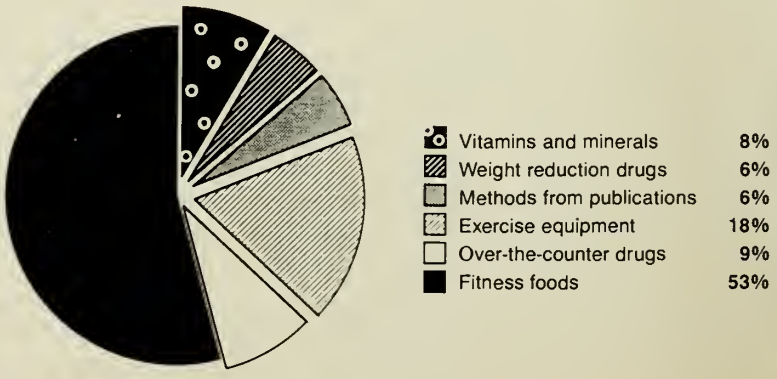

Figure 1.—Estimated costs of weight reduction in percentages of the total are shown in this pie chart (adapted from *US News and World Report,* December 1982 and Oct 8, 1984, pp 57-60; *Time,* Jan 20, 1986, pp 54-60: and Greenwood[2]).

is fraught with difficulties because of varying compliance with a diet. We know of no studies comparing weight loss of the same subject during inpatient and outpatient dieting. There are, however, data comparing different groups from the same clinic. When persons weighing on average 109 kg (240 lb) were admitted to a metabolic ward, they lost an average of 1.1 kg per week for the first four weeks while eating a diet containing 1,300 kcal per day. The comparable weight loss for a group prescribed a similar diet on an outpatient basis over four weeks averaged 0.5 kg per week. By implication, the actual quantities of energy ingested were about twice the prescribed level.[8]

A third aspect of any diet is its nutrient composition. The fraction of carbohydrate in the diet influences sodium metabolism. This in turn may be related to the effect of carbohydrate on the activity of the sympathetic nervous system and the concentration of triiodothyronine. Because the percentage of carbohydrate in the diet influences the concentration of triiodothyronine,[9] the major calorigenic hormone, it may be that carbohydrate plays an important role in modulating the metabolic rate.

Another element in the diet is the amount of nitrogen in relation to calories. When calorie levels are below those required to maintain body weight, a higher quantity of dietary nitrogen is required to minimize nitrogen loss.[10] A number of factors have been shown to influence the nitrogen balance in persons eating a low-calorie diet. These include the length of time over which the diet is consumed, the total energy available from the diet, and the ratio of fat to carbohydrate in the diet. The nature of the diet consumed before a new diet is initiated will influence nitrogen balance. If the nitrogen content of a weight-maintaining diet is low, less nitrogen will be lost when the caloric intake is reduced than if the diet were high in nitrogen. The work of Forbes suggested that the total body fat stores may also influence the rate of nitrogen loss.[11] Substantially overweight persons lose less nitrogen than those of normal weight when caloric intake is restricted. Finally, there are important differences between persons in nitrogen loss. Hood and associates have tested diets containing 3%, 6%, 12%, 25%, and 50% of energy from carbohydrate in a total caloric intake of 1,000 kcal (4.2 MJ).[12] Nitrogen equilibrium was not attained with any of these diets. Nitrogen loss, however, was less with diets having a high carbohydrate content than with the low carbohydrate (ketogenic) diets. Thus, ketosis does not have a protein-sparing effect. The longer a person is on a reducing diet, the smaller the daily nitrogen loss.

A final consideration in selecting a diet is the frequency with which food is eaten. Fábry and colleagues in Czechoslovakia have suggested that eating less than two meals a day is associated with an increased skin-fold thickness compared with that of persons eating more than two meals per day.[13] Studies by Bray and by Fábry and co-workers have shown that eating one or two meals per day is associated with an increased level of serum cholesterol compared with eating six or more meals per day.[13,14] Finally, Garrow showed that the amount of nitrogen lost on a fixed caloric intake is lower with five meals than with three or one, whether the diet contains 10%, 13%, or 15% protein.[6] It would thus seem desirable to eat five meals per day at whatever level of protein was selected.

Estimating Caloric Need

The rate of weight loss is directly related to the difference between energy intake and one's energy requirements. An average deficit of 500 kcal per day will produce an expected weight loss of 0.45 kg per week. Although there are several methods of estimating caloric expenditure, we suggest using body weight and the formula derived by Owen and colleagues.[15,16] This allows a direct estimate of the resting metabolic rate and a calculation of the daily energy requirement.

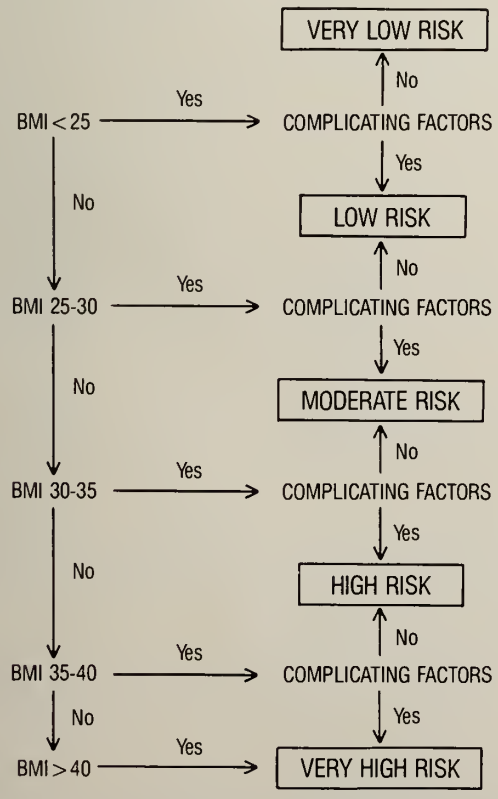

Figure 2.—A risk classification algorithm is shown, with the patient first placed into a category based on the body mass index (BMI). The presence or absence of complicating factors determines the degree of health risk. Complicating factors include elevated abdominal-gluteal ratio (men, 0.95; women, 0.85), diabetes mellitus, hypertension, hyperlipidemia, male sex, and age younger than 40 years.

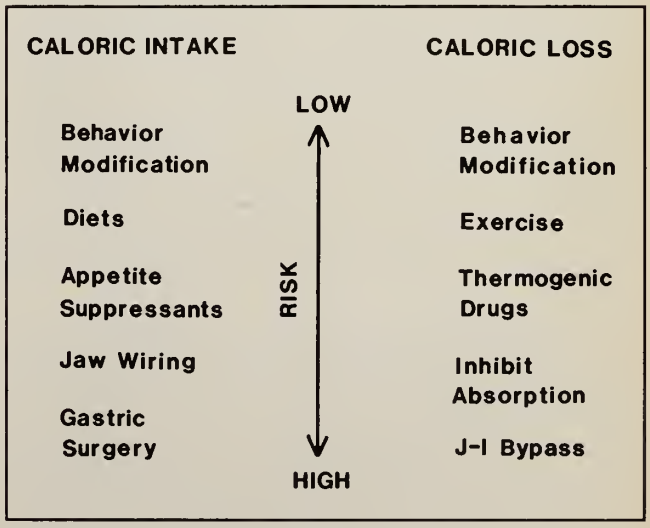

Figure 3.—Treatments for obesity are listed in relation to their risk. The group in the left column are those treatments that affect caloric intake and on the right those that affect caloric expenditure. J-I = jejunoileal

TABLE 1.—*Estimating Energy Needs*

Resting Metabolic Rate	*Daily Energy Requirement**	
	Activity Level	*Activity Factor*
Men = 900 + 10 × (Wt in kg)	Low	1.2
Women = 800 + 7 × (Wt in kg)	Moderate	1.4
	High	1.6

*Resting metabolic rate times the activity factor.

A low activity level includes persons who lead a sedentary life. A high activity level applies to people in jobs requiring manual labor or people with regular daily exercise programs (Table 1).

Conventional Diets

Conventional diets are defined as those below energy requirements but above 800 kcal per day. These diets fall into four groups: those with balanced low calorie levels, those that are predominantly low in carbohydrate, those that are low in protein, and those that might best be described as "fad diets." In this last category would be diets involving unusual combinations of food intake or eating sequences.

The first point about all 800-kcal (3.4-MJ) diets is that weight loss will occur and is predictable, given an estimate of energy expenditure and an adequate compliance with the diet. The second point is that measurements of energy expenditure using an indirect calorimeter have shown that those who claim to be "metabolically resistant" to losing weight in fact require more than 1,200 kcal per day; none have been found to require less. Third, the composition of weight loss on a low-calorie diet will depend on the duration of the diet and the nutritional state of the person at the beginning of the diet.

Fat stores provide the major source of fuel energy when caloric intake is below expenditure. During the adaptation to any calorically restricted diet, there is initially a greater loss of protein and water than later on. As long as intake is below energy requirements, however, there will be a continuing loss of nitrogen from protein breakdown. This is not surprising when one considers the composition of tissue accumulated during periods of weight gain. When weight increases as a result of overeating,[11] approximately 75% of the extra energy is fat, and the remaining 25% is lean tissue. If the lean tissue contains 20% protein, then 5% of the extra weight gain would be protein. It would thus be anticipated that at least 5% of weight loss would be protein. Thus, small continuing losses of protein are to be expected during weight reduction. Indeed, they are a necessary part of a calorie-reduced diet. The desirable feature of any reduced caloric intake, however, is that it provide the least possible loss of protein, recognizing that this cannot be less than 5% of the weight loss.

Planning a diet requires selecting the caloric intake and then selecting foods to meet this caloric level. Because it is desirable to ingest foods with adequate nutrients in addition to protein, carbohydrate, and essential fatty acids, diets should eliminate alcohol, sugar-containing beverages, and most highly concentrated sweets because these rarely contain adequate amounts of other nutrients besides energy.

We have developed a system for calorie substitution or exchange using a quality guide for assessing food choices. With this food choice system, foods are assigned to one of four categories—A, B, C, and D—depending on the relative quantity of nutrient compared to the energy density of the food. This system is based on information available in the US Department of Agriculture Handbook No. 8. Foods are divided into high- and low-calorie units based on calorie density. They have been further divided into A, B, C, and D, subgroups with high-quality foods given ratings of A and B and low-quality foods ratings of C and D. Dietary choices can then be made to select predominantly from the A and B foods, with less selection from the C and D foods. Table 2 provides a short list of some foods from each category for each of the food groups that we use.

The long-term success of treatment programs using nutritional advice alone is hard to quantify because many programs mix therapies. In one study with a 14-year follow-up, 27 of 32 patients were reexamined.[17] Of the 27, 5 (18%) weighed less than at the end of the original program with an average loss of 13 kg. In a seven- to nine-year follow-up of 19 obese women,[18] 9 weighed less than initially. In a five-year follow-up of 67 overweight persons initially weighing 89.2 kg (197 lb), Stamler and associates reported that the mean weight loss of 6% of initial body weight was achieved between one and two years and was maintained for five years.[19] The duration of success after treatment can be predicted by fat cell morphology. Patients with hyperplastic obesity did less well than those with hypertrophic obesity (to be discussed in more detail later).[20]

Very-Low-Calorie Diets

Very-low-calorie diets are those diets containing between 200 and 800 kcal per day; many such diets have been developed. For practical purposes, diets with energy levels between 200 and 800 kcal per day will be called very-low-calorie diets and those below 200 kcal per day starvation diets. Because the energy withdrawn from body stores is a function of the energy deficit, the lower the calorie intake, the more rapid the weight loss. Starvation produces the most rapid weight loss, but protein loss is a major drawback. To prevent this, diets composed predominantly of protein and containing 200 to 400 kcal were introduced in the 1970s.[21] A second approach to developing a very-low-calorie diet was to determine the quantity of nutrients that are desirable for human nutrition, with an energy level as low as practical. The *Recommended Dietary Allowances* (RDA)[22] is one basis for these needs. The RDA includes 0.8 gram per kg of protein per day. Using this figure, the minimum desirable protein intake would be 56 grams per day for a 70-kg (154-lb) man. With low caloric intake, however, a higher nitrogen intake may further reduce protein loss. For this reason, we selected 70 grams per day for protein. Carbohydrate at 50 grams per day minimizes ketosis and helps maintain circulating levels of triiodothyronine. With 10 grams of essential fatty acids added to the diet, we arrived at a diet of no less than 570 kcal per day. Some very-low-calorie diets use predominantly fish and fowl to provide the foods for the diet. Alternatively, various formulas use artificial protein sources (usually casein, soy protein, or egg protein) with various added nutrients.

An early catastrophe with formula diets occurred when one containing collagen as the sole source of protein was sold widely to the American public. Data on 16 women and 1 man who died while consuming this diet were reported by the Centers for Disease Control.[23] The 16 women had lost an average of 37.7 kg (83 lb) at a rate of 2.1 kg (4.6 lb) per

week, which represented 34% of their body weight. Six women died outside the hospital, and another six died after being admitted for syncopal events. The remaining four had cardiac arrests outside the hospital. Ventricular tachycardia and fibrillation were documented in ten of the women. It became clear that long-term adherence to a diet with low-quality protein could be hazardous to the cardiovascular system of otherwise healthy persons. In the past ten years,

TABLE 2.—*Subdivision of Foods Within Each Food Group Based on Relative Nutritional Value**

A	B	C	D
Vegetables and Beans			
Asparagus	Beans, yellow	Beans, lima	Beans, white
Broccoli	Brussel sprouts	Beets, red, cooked	Corn, on or off the cob
Chard, Swiss	Cauliflower	Cabbage	Lentils
Beans, green	Celery	Carrots	Pickles, sweet
Kale	Cucumbers	Coleslaw	Potatoes, French fried, scalloped with cheese, mashed from flakes
Lettuce	Peppers, green or chili	Kohlrabi	
Mustard greens	Pickles, dill	Onions	
Okra	Pumpkin, raw	Peas, green	
Parsley		Pickles, sour	
Spinach		Potatoes, raw, baked, or boiled	
		Pumpkin, canned	
		Rutabagas	
		Squash, winter, acorn, butternut	
		Sweet potatoes	
		Turnips	
Meat, Fish, and Poultry			
A	B	C	D
Meat			
Beef, arm pot roast	Beef, round, dried and cooked	Bacon, Canadian	Bacon, cured
Flank steak	Lamb, leg	Beef, rib	Beef, chuck, ribs
Hamburger, lean	Liver, calf	Pork, picnic, spareribs	Porterhouse steak
Pork, fresh ham, lean only	Pork, fresh loin	Lunch meat, meat loaf	T-Bone steak
Sausage, liverwurst	Rib (lean)	Sausage, Polish style, salami	Club steak
Veal, chuck			Rib eye
			Corned beef hash
			Lamb, loin, rib
			Sausage, blood, Bratwurst, bologne, frankfurters, pork
Fish			
Abalone	Pompano	Lobster Newburg	
Clams, raw meat	Salmon, fresh	Oysters (high sodium)	
Crab, steamed	Shad	Shrimp	
Halibut	Haddock, fried	Tuna in oil	
Mussels	Mackerel		
Whitefish	Smelt		
Lobster	Ocean perch		
Pollack	Bluefish		
Rockfish	Tuna in water		
Snail			
Sturgeon			
Swordfish			
Cod, raw, fresh			
Flounder			
Scallops			
Poultry			
Chicken, light meat, breast	Chicken, dark meat, drumstick, liver	Chicken a la king	
	Eggs, any style		
	Turkey, roasted, light or dark meat		
Milk and Cheese			
A	B	C	D
Buttermilk	Milk, 2% fat	Milk, whole	Cheese, blue, Camembert, or cream
Skim	Cheese, cottage (3.7%), low fat	Margarine	Cream, whipping, half-and-half
	Yogurt, low fat	Cheese, cottage (cream), cheddar (American), processed American	Ice cream, regular or rich
		Yogurt, whole milk	
		Ice milk	

*Within each food group, foods were allocated into **A**, most nutritious, through **D**, least nutritious, using the relative percentage of nutrients in each food compared to the energy content of the food.

formula diets containing high-quality protein (casein, egg albumin, or soy) as well as carbohydrate and adequate quantities of other nutrients, especially potassium, magnesium, vitamins, and minerals, have been used with no recurrence of these arrhythmias.[24]

Weight loss with very-low-calorie diets is more rapid than with conventional diets because the caloric intake is lower and because compliance may be easier. In studies of as long as 20 weeks in duration, the rate of weight loss appears to be related directly to the duration of treatment and averages 1.5 kg or more per week (Figure 4).[25]

As with all diets, the weight loss initially contains a larger quantity of protein than after adaptation, when protein breakdown slows. Patients adhering to very-low-calorie diets usually have a reduction in blood pressure, with the most rapid drop occurring during the first week.[21] The use of antihypertensive medication, especially drugs influencing ionic mechanisms such as calcium channel blockers and sodium-potassium exchange in the kidney, should usually be discontinued at the beginning of a very-low-calorie diet. Most diabetic persons on very-low-calorie diets experience a notable abatement of their diabetes. Blood glucose levels drop within the first couple of weeks and remain low for as long as the diet is continued. Those taking less than 50 units of insulin or oral hypoglycemic drugs will usually be able to discontinue the use of these medications.

A number of side effects have been noted with very-low-calorie diets, including hair loss, thinning of the skin, and coldness.[21] Because severe caloric restriction is undesirable for lactating and pregnant women, these diets are contraindicated for that group as well as for children, who are still requiring protein for growth. Finally, as with all diets, there is increased cholesterol mobilization from peripheral fat stores, enhancing the quantity of cholesterol moving through the biliary system and increasing the potential risk of gallbladder stones.

Starvation

Starvation is the ultimate very-low-calorie diet and is defined as an intake of less than 200 kcal per day.[26] With no calories, the loss of protein and cellular components is rapid. The rate of weight loss is also rapid, but 50% or more of this initial loss represents fluid, and thus problems with hypotension are not uncommon. Likewise, a rise in the serum uric acid level increases the risk of precipitating gout or renal uric acid stones. Because weight regain following starvation occurs in a high percentage of patients and starvation must be conducted in a carefully supervised medical setting, its use has largely disappeared except under experimental circumstances.

Behavioral Treatment

Behavior Modification

The work of Stuart more than 20 years ago revolutionized the treatment of obesity. Using the concepts of Ferster and colleagues,[27] Stuart reported an uncontrolled treatment program in which 11 subjects were enrolled and 8 women completed the study.[28] During the year of treatment, the eight women lost an average of 17.2 kg (40 lb). Initially subjects were seen individually for 30 minutes three times per week for the first four to five weeks and then twice a week for three months. The results reported by Stuart were more impressive than those documented in subsequent studies. Behavioral treatment remains a main component of most weight loss programs, however.

Behavioral treatment of obesity can be broken down into three categories.[29,30] The first is self-monitoring, or what might be called the measurement of antecedents. This self-monitoring identifies settings in which eating occurs by writing down the kinds of food eaten, the places where they are eaten, the frequency at which they are eaten, and the emotional setting in which they are eaten. Using these self-monitoring reports, persons can identify antecedent problems related to times and places of eating that they may be able to change.

The second component of behavior modification involves stimulus control, or breaking the chain of events between an antecedent for eating and the eating event itself. A number of techniques have been developed to provide stimulus control. Among the simplest are restricting the number of eating places or the utensils used for eating. Others involve picking up a glass of water between each bite, chewing food a defined number of times, excusing oneself from the table for periods of time, and so forth. The goal is to separate the events that trigger eating from the eating itself.

The third component of behavior modification involves techniques for self-reward, for assertiveness training, for developing positive "self-talk," and for developing rewards for changing behavior.

A number of reviews of the literature of behavioral management have been published.[29-31] From these, several general conclusions can be drawn about weight loss programs using behavior modification. The weight loss at the end of treatment averages 4.5 to 5.4 kg (10 to 12 lb) for programs that average 8 to 12 weeks in duration. A year after completing treatment, there is on average little further change in body weight. Long-term maintenance of the weight loss appears to be better in programs that use behavioral treatment. The attrition rate during treatment may be 20% or less, which is significantly below the 25% to 75% reported from most other types of treatment. The skill and experience of therapists has varied considerably but is probably important. In a comparison of five therapists using a similar behavioral

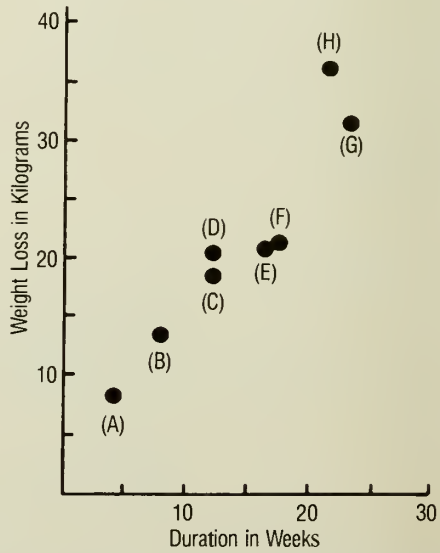

Figure 4.—The amount of weight loss in relation to duration of treatment is presented for several very-low-calorie diets. The letters in parentheses represent specific programs described by Wadden and co-workers.[25]

program as part of a multicenter drug trial,[32] we noted that patients treated by two physicians showed no significantly greater weight loss than those treated by three nonphysicians. One nurse, however, was significantly less effective with her group than the other two nonmedical therapists.

In a one-year follow-up of 590 patients, Foreyt noted an average weight loss of 5.8 kg (12.8 lb) (oral communication, June 1987). Of the 590 persons, 18% were either at or above their entry weight after a year. At follow-up of 426 patients five years later, the mean weight loss at the end of treatment was 6.9 kg (15 lb) in 116 men and 4.2 kg (9 lb) in 310 women. At one year in this group, it was 7.4 kg (16 lb) for the men and 5.4 kg (12 lb) for the women. At five years, the weight loss was 6.3 kg (14 lb) from the beginning for the men and 4.3 kg (9½ lb) for the women. Thus, 50% maintained or continued to lose weight. The relative importance of behavioral techniques, whether alone or combined with other programs, is clear from a review of the literature.

Work-Site Programs

Stunkard and Brownell have applied the techniques of behavior modification for the treatment of obesity to the work site.[33] Attrition was a major problem, as it has been in most outpatient treatment programs. The dropout rate, however, was lower in groups led by lay therapists than in groups led by a professional therapist. Weight loss did not differ between groups and was 3.6 kg (8 lb) in those completing a 16-week program.

Self-Help Programs

A number of self-help groups for weight control now exist in the United States and other countries.[34] Among these are noncommercial groups such as Take Off Pounds Sensibly (TOPS) and Overeaters Anonymous and commercial groups such as Weight Watchers International, Diet Workshop, Diet Center, and other programs. Studies on these groups and their effectiveness are limited, but it is clear that attrition is a major problem.[35] In a study of the TOPS clubs, 350,000 members in 12,000 chapters were studied. Almost all were women. Among the features of the weekly meetings was the official weigh-in and announcement of individual changes in weight. In studying 21 chapters in the Philadelphia area, Garb and Stunkard noted that the mean weight loss was 6.8 kg (15 lb) per member, with a standard deviation of 6.8 kg.[36] When the same chapters were reviewed two years later, the mean weight loss was 6.4 kg (14 lb) and the standard deviation 7.7 kg (17 lb). The rate of attrition of the TOPS clubs and several other groups ranged from 40% to 70%. The time when half the clients stop attending varies between 10 and 50 weeks. In a comprehensive survey of weight losses in Weight Watchers groups, Ashwell and Garrow noted that on average, patients in these groups in the United States lost 11.8 kg (26 lb) in 30 weeks.[37] Attrition obviously includes those who successfully achieve their weight goal and those who do not. Available data do not allow us to distinguish between them.

Psychoanalysis

Psychoanalysis has also been used for the treatment of obesity. In a retrospective study,[38] 72 psychoanalysts collected information on 84 obese patients and a control sample of 63 of their patients who were of normal weight. While obesity was the chief complaint of only six of these patients, weight losses at 42 months of psychoanalytic treatment compared favorably with those after traditional medical efforts. Of those obese patients receiving psychoanalytic treatment, 39 (46%) lost more than 9 kg (20 lb) and 16 (19%) lost more than 18 kg (40 lb). There was also a striking decrease in the percentage of obese patients suffering from a disparagement of their body image. This declined from 40% to 14%, an unexpectedly good result for this chronic and intractable disorder. Thus, behavioral treatments ranging from psychoanalysis to work-site programs to family and couples training and clinical approaches offer notable contributions to short- and long-term effectiveness in treating obesity.

Effects of Exercise

Effects on Food Intake

Studies on the effects of physical training on food intake in humans are limited. Leon and co-workers noted a reduction in caloric intake in six obese men who walked five days per week for 90 minutes at a 10% grade, which provided an estimated expenditure of 1,100 kcal per session.[39] No diet was prescribed. Baseline caloric intake using a three-day dietary record was 2,288 kcal per day. During the initial phase of exercise, caloric intake increased to a value of 2,459 kcal per day by the 8th week but had declined to 2,149 kcal per day by the 16th week of the program. The most incisive studies, however, have been done by Woo and colleagues, who examined the effects of sedentary, mild, and moderate levels of energy expenditure on daily caloric intake in obese and lean subjects.[40] In the lean subjects, there was a compensatory increase in food intake as energy expenditure increased, and thus body weight was maintained. In the obese subjects, however, there was inadequate compensation. Energy intake increased slightly from 2,233 kcal per day in the sedentary state to only 2,346 kcal per day at the low level of energy expenditure (10% above sedentary). When exercise was 25% above sedentary levels, food intake was 2,303 kcal per day, only 70 kcal above sedentary. As anticipated, the obese subjects lost weight during the period of exercise because the increase in food intake was inadequate to meet the extra needs. We would suggest that increased energy expenditure of moderate degrees in obese subjects may not be accompanied by any change in their level of food intake.

Effects on Body Composition and Function

The process of adapting to endurance exercise involves a number of changes that enhance the ability to oxidize fatty acids. There is an increase in the maximal capacity to consume oxygen. In addition, an increased cardiac output can result in a greater delivery of blood and oxygen to muscles. There is a concurrent increase in the activity of muscle enzymes that oxidize fatty acids involving primarily the red or high-capacity oxidative fibers in muscle. Physical training may also reduce the total quantity of body weight and body fat. Wilmore reviewed a large number of studies on the effects of exercise on body composition.[41] Most of these were training programs lasting from 7 to 22 weeks. The changes in body composition were surprisingly small. On average, body fat decreased by only 1.6%, and, in 5 of the 55 studies, there was actually a rise in body fat after training. Moreover, lean body mass fell in 17 of these 55 studies. During exercise in moderately obese subjects as opposed to persons of normal weight, there is a decrease in the body fat that can be more readily shown. In 12 studies of overweight men and women, the mean decrease in body weight ranged between 2.6 and 14.3 kg (6 to 31 lb), with most of this loss being accounted

for by a decrease in body fat.[41] In a 12-week exercise program involving 23 obese and 13 lean women, Franklin and colleagues noted a decrease of 2.6 kg in body weight in the obese women, with no significant change of weight in the lean women.[42]

The amount of weight loss also appears to be related to the amount of exercise done. In a study of normal weight men, Pollock and associates were able to show an increase in exercise capacity from 20-week exercise programs involving training sessions two and four days per week.[43] Only the men exercising four days per week showed significant decreases in body weight. In a study from Bulgaria, 23 obese women in an inpatient treatment program who exercised an average of ten hours per day over 45 days lost an impressive 12.4 kg (27 lb).[44] The weight lost was almost entirely fat because there was no significant change in lean body mass. It is clear that exercise alone can decrease body weight. Even though losses may be greater in the obese than in the lean, however, they are generally not greater than 2.4 kg,[41] the 12.4 kg noted above being the exception.

In contrast with these data on persons of moderate obesity—a BMI of 35 kg per m^2—a reduction in body fat after physical training is difficult to show in massively obese persons. When eight massively obese patients weighing on average 112 kg (247 lb) underwent a physical training program lasting three to six months with three-times-a-week sessions, neither body weight nor body fat content decreased.[45] In the same laboratory, however, a similar conditioning program reduced body fat in normal weight persons. The degree of weight loss in the moderately obese appears to depend on the size and number of fat cells.[46] A reduction of body fat content during physical training is accompanied by a decrease in the average size of fat cells (0.5 to 0.41 μg lipid per cell). Persons with larger fat cells (hypertrophic obesity) may lose more fat during an exercise program than those with a larger number of relatively smaller fat cells (hyperplastic obesity). This suggestion was supported by a study of 27 obese women that showed a negative correlation between weight loss and fat cell number.[18] That is, the women with fewer fat cells lost weight during an exercise program, while those with hyperplastic obesity actually tended to gain weight.

Intensive and prolonged physical training modifies the metabolism of glucose, insulin, and lipids in obese persons. During physical training, glucose tolerance improves and the insulin levels are significantly lower, suggesting an increased effectiveness of insulin on the metabolism of glucose. Exercise in normal weight persons can be associated with an increase in high-density lipoprotein (HDL) levels. In obese persons, however, changes in lipid metabolism with exercise are more complex. Obesity is usually associated with reduced circulating levels of HDL cholesterol.[47] Brownell and colleagues have reported that a 10.7-kg (24-lb) weight loss in men was associated with a 5% increase in the HDL cholesterol level. There was also a 15.8% decrease in the low-density lipoprotein (LDL) cholesterol level and thus a 30% increase in the ratio of HDL to LDL cholesterol. In women, on the other hand, a weight loss of 8.9 kg (20 lb) produced no significant change in HDL-cholesterol levels.

Exercise and Caloric Restriction

The addition of regular exercise to programs involving moderate to severe calorie restriction has failed to show any increase in weight loss. Warwick and Garrow compared three women who were observed for 12 weeks on a metabolic ward while on a reducing diet containing 800 kcal (3.4 MJ) per day.[49] These authors were unable to find any increase in weight loss when subjects bicycled for two hours a day compared with when they did no additional exercise. They similarly found no effects of physical training on nitrogen balance and suggested that the failure to lose weight despite the greater energy deficit caused by exercise may have been due to glycogen deposition in trained muscles. This finding was confirmed by Hill and co-workers, who compared five obese women who participated in walking up to 6 km per day with three who did no exercise during an inpatient study in which all subjects received an 800-kcal liquid diet each day.[50] Both groups lost approximately 8 kg. The only significant difference was that the group that exercised lost more fat and less lean body mass than the group that did not. Pavlou and associates randomly assigned to exercising and nonexercising groups moderately obese police officers (all men) who were on a variety of reduced calorie diets.[51] The officers who exercised for 20 to 45 minutes three times per week at 85% of their maximal heart rates showed no greater weight loss—11.8 kg versus 9.2 kg (26 lb versus 20 lb)—but lost significantly more fat and less lean body mass than the group not exercising. Other studies, however, have failed to show a sparing of lean body mass by exercise during caloric restriction. Van Dale and colleagues randomly assigned 6 of 12 obese women who were on a 12-week restricted diet of about 800 kcal per day to exercise for one hour, four days per week at 50% to 60% of their maximum aerobic capacity.[52] Both groups lost 12 to 13 kg (27 to 29 lb), but there was no difference between them in the loss of body weight, fat, or lean body mass. Thus, it appears that exercise will not increase the rate of weight loss during a period of calorie restriction, though the reasons for this are not clear. Furthermore, there is a strong suggestion that exercise may spare the loss of lean body mass during diet-induced weight loss, though research is contradictory on this point. Such factors as age, sex, type and quality of diet, and frequency and intensity of exercise may explain some of the discrepancies, and more research is needed to clarify this issue.

Long-term Maintenance of Weight Loss

Several studies with long-term follow-up have suggested that including exercise in a weight control program leads to improved long-term results. Harris and Hallbauer studied 35 women and 11 men in a program that lasted for 12 weeks and used behavior modification and a contingency contract with or without daily exercise.[53] Weight losses ranged from 2.0 to 3.2 kg (4 to 7 lb) and were not significantly different from those in a control group. When the subjects were examined six months later, however, the control subjects showed a net gain in weight of 0.8 kg (1.8 lb), while both of the other groups continued to lose weight after completing the program. The exercise group's weight loss of 4.0 kg (9 lb) was significantly greater than the 2.9-kg (6-lb) loss of the group not exercising. After a year of follow-up, Stalonas and associates noted a nonsignificant trend for greater weight loss in a behavior modification and exercise group compared with subjects treated only with behavior modification.[54] Weight losses ranging from 4.3 to 6.0 kg (9½ to 13 lb) did not differ between groups at the end of the initial ten-week program. More recently, Dahlkoetter and colleagues studied 44

women who were at least 6.8 kg (15 lb) above ideal weight.[55] Those using only behavior modification lost 3.2 kg, which was slightly more than in those treated with only exercise. Those who received a combination of exercise plus behavior modification lost an average of 6.1 kg (13 lb). At follow-up six months later, those in the exercise-only group were 2.5 kg (5½ lb) lighter than initially, having gained 0.3 kg from their minimum. Those in the behavior modification group showed no change from the end of treatment, and those treated with exercise plus behavior modification increased their weight loss to 7.3 kg (16 lb), for an additional loss of 1.1 kg (2½ lb). Thus, while adding exercise to a calorie-restricted diet does not increase the rate of weight loss, there is some suggestion that exercise training as part of the treatment of obesity might improve results over the long term.

Drug Therapy

Appetite-Suppressing Drugs

Drugs acting on catecholamine neurotransmitters. Most appetite-suppressing drugs possess many of the pharmacologic properties of the naturally occurring neurotransmitter norepinephrine, and all of the drugs listed in Table 3 can stimulate the central nervous system and increase locomotor activity.[56] Their relative potencies, however, differ considerably.

The pharmacologic effects of appetite suppressants can be divided into three categories: First, most of these drugs can stimulate the central nervous system, but this is highly variable. Amphetamine and methamphetamine are moderately potent and are addictive. Second, appetite-suppressing drugs have cardiovascular effects, including a rise in heart rate and blood pressure. The hypertensive effects of tyramine and norepinephrine may be aggravated during the initial administration of amphetamine, but with continuous administration, amphetamine has less of an effect on the blood pressure. A rise in the heart rate and blood pressure has occurred with the use of amphetamine sulfate, methamphetamine hydrochloride, ephedrine, phenmetrazine hydrochloride, and methylphenidate hydrochloride, but other drugs listed in Table 3 have few of these effects. Third, metabolic effects expressed as a rise in the concentration of free fatty acids or glycerol (or both) in plasma have been observed after the administration of amphetamine, methamphetamine, and phenmetrazine. Methamphetamine has been found to antagonize the lipolytic effects of norepinephrine in vitro but has no direct lipolytic effect itself. Mazindol has been reported to increase the uptake of glucose following its intra-arterial administration in humans.

The peak blood concentration usually occurs shortly after the oral administration of appetite-suppressing drugs, but their half-life in the serum varies considerably. There are also important pharmacologic differences in stereoisomerism among these compounds. The dextroisomer of amphetamine, for example, is four times more potent than the levoisomer. The D-isomer of fenfluramine appears to contain all of the appetite-suppressing effects of fenfluramine, with the L-isomer being ineffective in this regard. The urinary excretion of several drugs depends on the urine pH.

In evaluating the clinical usefulness of appetite suppressants, two questions need to be answered: Are they effective? and Are they safe? The Food and Drug Administration has provided one of the largest reviews of their effectiveness,[57] analyzing 105 new drug applications containing data about 4,543 placebo-treated patients and 3,182 patients treated with active drugs. In studies comparing placebo and active drugs, the dropout rate after four weeks of therapy

TABLE 3.—*Appetite-Suppressing Drugs*

Generic Drug and Some Proprietary Names	*Supplier*	*Dosage, mg*	*Administration, mg*	*Peak Blood Concentration, hours after oral dose*	*Half-life in Blood, hours*	*Excreted Unchanged in Acidic Urine, %*
Schedule II*						
(+)-Amphetamine sulfate		5, 10, 15	5 to 10 before meals (tid)	1-2	5	55
Methamphetamine HCl		5, 10, 15	2.5 or 5 before meals (tid)	1-2	13	45
Desoxyn	Abbot		10 or 15 in morning			
Phenmetrazine HCl		25, 50, 75	25 bid or tid	...	...	19
Preludin	Boehringer Ingelheim					
Schedule III*						
Phendimetrazine tartrate		35	35 before meals	...	4	??
Plegine	Ayerst					
Benzphetamine HCl		25, 50	25-50 before meals	1-2	...	??
Didrex	Upjohn					
Schedule IV*						
Diethylpropion HCl		25, 75	25 before meals (tid)	1-2	8-13	24
Tenuate	Merrell Dow		75 in morning			
Tepanil	Riker					
Fenfluramine HCl		20	20-40 before meals	1	20	20
Pondimin	Robins					
Mazindol		1, 2	1 before meals	2	13	22
Sanorex	Sandoz		2 in morning			
Mazanor	Wyeth					
Phentermine		15, 30	15 tid	...	Free 7-8	75
Fastin	Beecham		30 in morning			
Ionamin (resin)	Pennwalt			1	20-24	

bid=twice a day, HCl=hydrochloride, tid=three times a day

*The Federal Controlled Substances Act of 1970 places the prescription anorexiants into five schedule categories going from high abuse potential (Schedule I) to low abuse potential (Schedule V).

was 18.5% for subjects receiving a placebo and 24.3% for those receiving an active drug. At the end of the study periods, lasting three, four, and eight or more weeks, equal percentages of patients receiving placebo and active drugs remained in treatment (49% for placebo versus 47.9% for active drugs). Drug-treated patients lost on average 0.25 kg (0.56 lb) per week more than subjects receiving placebos. In clinically effective doses, there was no basis on which to choose between these drugs in terms of patients' rates of weight loss or the duration over which this weight loss occurred.

Additional data are available from trials lasting from 6 to 52 weeks (Table 4). Often more than 60% of these patients have remained in the trials.[58] Weight loss continued for the duration of treatment, and tolerance of the drugs apparently did not develop. If tolerance had developed, we would expect the drugs to lose their effectiveness or increased dosages to be required to maintain weight loss. This does not seem to occur. In one trial, fenfluramine hydrochloride was administered continuously for a year, followed by a second year of administering a placebo.[59] A plateau of weight loss occurred between the 8th and 12th months, and weight remained 10 to 11 kg (22 to 24 lb) lower for the remainder of the year. When transferred to receiving a placebo, patients regained weight. One interpretation of this is that the drug had reset part of the weight-control mechanism and that this effect persisted for the entire year.[60] Three clinical findings from this study would argue against tolerance: subjects regained weight

TABLE 4.—*Double-Blind Clinical Trials With Appetite-Suppressing Drugs**

Drug	Dosage, mg	Duration, wk	Number of Subjects		Mean Total Weight Loss (Gain), kg		Net Weight Loss, kg	Diet Restriction, kcal/d
			Drug	Placebo	Drug	Placebo	(Drug)-(Placebo)	
Schedule II								
Amphetamine sulfate	5 tid	12	14	12	4.5	2.4	2.1	...
	5 tid	6	20	21	1.5	0.5	1.0	1,000
	5 tid	12	32	33	6.0	2.6	3.4	1,000
Phenmetrazine HCl	75	6	53	53	1.8	0.6	1.2	None
	75	12	24	0	2.8	NA	NA	None
	25 bid	6	27	0	2.6	NA	NA	None
	50	6	28	0	2.0	NA	NA	None
	25 tid	6	14	12	3.9	1.2	2.7	...
Schedule III								
Phendimetrazine tartrate	105	12	36	35	3.4	0.5	2.9	None
Schedule IV								
Diethylpropion HCl	75	6	28	28	1.9	0.9	1.0	1,200
	75	12	23	21	6.7	4.1	2.6	Restricted
	25 tid	12	41	41	9.1	4.5	4.6	1,000
	75	25	9	4	11.7	1.6	10.1	"Strict"
	25 tid	12	22	19	4.4	1.6	2.8	1,000
	25 tid	12	21	17	6.8	4.4	2.4	1,000
Fenfluramine HCl	20 bid	6	44	43	2.4	0.3	2.1	None
	40	6	23	43	1.7	0.3	1.4	None
	20 tid	12	17	0	7.4	NA	NA	1,000
	60	12	16	0	7.9	NA	NA	1,000
	20 tid	12	56	58	6.6	2.5	4.1	None
	60	12	60	58	4.7	2.5	2.2	None
Mazindol	2	12	50	43	8.6	5.4	3.2	600
	1 tid	6	18	21	2.3	0.5	1.8	1,000
	1 tid	6	15	12	5.1	1.2	3.9	...
	1 tid	12	32	33	6.4	2.6	3.8	1,000
	1 tid	6	30	30	4.6	1.7	2.9	None
	2	12	15	15	6.9	1.6	5.3	1,200
	2	12	40	20	8.4	1.2	7.3	1,000
	2	12	27	24	8.5	6.5	2.0	1,000
	2	12	19	23	1.4	0.3	1.1	Restricted
	1 tid	8	12	13	5.2	3.8	1.4	1,200
	1 tid	12	12	9	5.2	0.5	4.7	None
	2	12	19	23	5.0	3.6	1.4	5-10/lb body wt
	1	60	11	10	14.8	10.5	4.3	800
	1-3	20	24	24	1.9	(0.7)	2.6	1,200
	1	6	15	15	1.2	(0.5)	1.7	†
	2	12	23	21	5.5	2.3	3.2	50 grams
Phentermine	30	16	34	36	9.2	5.2	4.0	9/lb body wt
	30	14	30	29	7.3	1.8	5.5	1,000
	30	6	78	77	3.8	1.5	2.3	1,000
	30	24	34	32	5.3	1.5	3.8	...

bid=twice a day, HCl=hydrochloride, NA=not applicable, tid=3 times a day, ...=data not available

*Adapted from Sullivan and Comai.[58]
†All patients were under dietary supervision for diabetes mellitus.

when fenfluramine use was discontinued; weight loss continued for six months until a new plateau was reached; and, hunger did not increase during several months of treatment.

The safety of appetite suppressant drugs has been the subject of considerable discussion. Griffiths and colleagues, using baboons as subjects, examined the reinforcing properties of intravenous preparations of several appetite-suppressing drugs and compared them with the effects of reducing food intake.[61] The ratio of anorexiant dose to reinforcing dose, a measure of abuse potential, is shown for several drugs in Figure 5. At one extreme are diethylpropion hydrochloride and amphetamine. At the other are fenfluramine and phenylpropanolamine hydrochloride.

Although the ratio of appetite-suppressing dose to reinforcing dose is of some use in predicting the potential for abuse, it does not always correlate with clinical experience. For example, diethylpropion has been widely used as an appetite-suppressing drug, yet episodes of misuse are few. Its appetite-suppressant-to-reinforcing ratio, however, is greater than that of amphetamine sulfate or phenmetrazine hydrochloride, both classified as Schedule II drugs. The prescribing of appetite suppressants is subject to the sanctions of the Federal Controlled Substances Act of 1970. Medicinal products subject to abuse are classified into five schedules based on accepted medical use and the potential for abuse. There is no indication for using drugs in Schedule II (relatively high potential for abuse; Table 3) for the treatment of obesity. Drugs in Schedule IV (low potential for abuse) are obviously preferred, but drugs in Schedule III also have a low abuse potential.

Drugs acting on serotonin neurotransmitters. One of the general biobehavioral properties of serotonin is to reduce the physiologic level of activity. Included in this is a reduction in food intake. Drugs modulating the system for serotonin metabolism have been shown to influence body weight.[62] Administering tryptophan or 5-hydroxytryptophan, the two precursors of serotonin that can enter the brain and be converted to serotonin, has been shown to reduce food intake. Similarly, drugs that release serotonin from nerve endings or

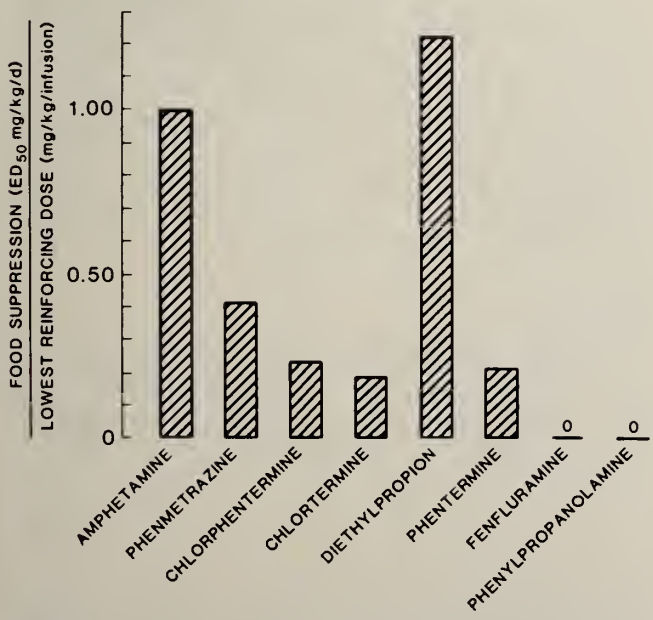

Figure 5.—The graph shows the anorectic-reinforcement ratio for several anorectic drugs. The greater the ratio, the greater are the reinforcing potential and probable abuse potential (from Hudson[59]).

block its reuptake have been shown to reduce food intake and to decrease body weight. Fenfluramine was the first clinically applied drug of this type. Other drugs have since been tested, and one drug in particular, fluoxetine,[63] has been shown to produce clinically effective changes in body weight, whether expressed in terms of absolute weight loss or weight loss relative to the initial weight. The relative effectiveness of fluoxetine compared with the D-isomer of fenfluramine (D-fenfluramine) remains to be determined.

Phenylpropanolamine. Phenylpropanolamine hydrochloride is one of the over-the-counter drugs that are available for weight control. It is also a component of many nasal decongestants. In a review of this drug, the advisory panel to the Food and Drug Administration concluded that it was probably safe and effective. In a critical review of published and unpublished studies of this drug, Weintraub supports this conclusion.[64] In a group of five clinical trials using only phenylpropanolamine, the drug-treated persons lost an average of 0.24 kg per week more than the placebo-treated group. This is similar to the difference between prescription appetite-suppressing drugs and placebo noted earlier.

Phenytoin. Compulsive or binge-eating patients provide an unusual clinical problem. They tend to eat large quantities of food at one time, a so-called binge, with periods of normal eating in between. The possibility that phenytoin might be effective in treating binge eating was originally proposed by Green and Rau.[65] They showed that ten patients with compulsive eating disorders and abnormal electroencephalograms could be separated from other types of obese persons. Using a questionnaire to identify such persons, Wermuth and co-workers were able to show that phenytoin was a useful drug for treating persons with compulsive eating disorder.[66]

Opioid antagonists. Clinical observations that single doses of naloxone hydrochloride could reduce food intake[67] led to several trials of naltrexone, a longer-acting opioid-blocking drug. In none of four published studies were there any consistent significant effects of the use of naltrexone.[68-71] In one trial, however, in which the higher dose of 300 mg per day was used, there were significant alterations in hepatic function, leading to a discontinuation of the trial of these drugs.[68]

Thermogenic Drugs

Thyroid hormone. One prototype of a thermogenic drug is the thyroid hormone, which produces a dose-related increase in metabolic expenditure. Pharmacologic doses of thyroid hormone are associated with an increased breakdown of protein, an increased calcium loss from bone, and an increased risk of cardiovascular dysfunction. There is, thus, no indication for using thyroid hormone in obese persons except as replacement therapy for clinical and laboratory-documented hypothyroidism.

Despite these drawbacks, however, interest in triiodothyronine (T_3) for treating obesity has been revived by two observations. First, during caloric restriction or low-carbohydrate diets, the concentration of T_3 falls.[9] Second, administering triiodothyronine can prevent the decline in the metabolic rate that occurs during treatment with very-low-calorie diets.[72] As much as 75% of the extra weight loss produced by T_3, however, can be accounted for by the loss of fat-free mass.[73] Moreover, the reduction in T_3 levels when dieting with a very-low-calorie diet may facilitate the conservation of visceral proteins. Thus, its use at present is experimental.

Ephedrine. Ephedrine is a synthetic adrenergic drug that can increase energy expenditure when administered orally. Its potential for weight loss was first described by Eriksen in 1972,[74] who noted that persons with asthma being treated with a compound containing ephedrine, caffeine, and phenobarbitol lost weight. Additional studies with ephedrine have had contradictory results. In a double-blind evaluation of the use of ephedrine and caffeine against placebo and diethylpropion (25 mg three times a day), Malchow-Moller and colleagues noted that during the 12-week study the mean weight loss was 4.1 kg (9 lb) in the placebo-treated group compared with 8.4 kg (18½ lb) in those treated with diethylpropion and 8.1 kg in those treated with the drug containing ephedrine.[74] The differences between active compounds and placebo were significant, but there was no significant difference between the use of diethylpropion or ephedrine.

Two separate studies have been conducted by Pasquali and associates.[75] In a 12-week trial involving unselected obese subjects, this group concluded that ephedrine at doses of 75 to 150 mg per day was ineffective when compared with placebo. More recently, however, Pasquali and co-workers have concluded that ephedrine may have some mild effect in obese subjects selected for resistance to previous attempts at weight loss.[76] The data at present are insufficient to conclude that ephedrine alone is useful in treating obesity.

β-Agonists. The observation that β-adrenergic drugs could enhance thermogenesis in experimental animals has led to the development of several compounds.[77] The experimental treatment of animals with these drugs will decrease body weight and body fat content without reducing food intake, suggesting that they work by increasing energy expenditure. Preliminary clinical trials suggest clinical effectiveness.

Dinitrophenol. Dinitrophenol is a toxic compound that uncouples oxidative phosphorylation.[7] It was used more than 50 years ago but abandoned because of the development of neuropathy and cataracts.

Drugs Affecting the Gastrointestinal Tract

Because the taste of food, its digestibility, and its metabolism are related to the control of food intake, it is not surprising that these approaches have been selected for the development of therapeutic drugs. Several different drugs that modify the digestive or absorptive processes in the gastrointestinal tract have been tested.

Benzocaine. Benzocaine, a topical anesthetic that can anesthetize the mouth or upper gastrointestinal tract, has been claimed to be effective by a review panel reporting to the Food and Drug Administration, but clinical data on this compound are limited.

Fiber. Fiber, which includes the cell-wall polysaccharides such as alginates, gums, hemicellulose, and lignin and which resists hydrolysis by human gut enzymes, has been suggested as a therapeutic agent in obesity because it can cause gastrointestinal distention. Data on the use of methylcellulose are conflicting. In one trial, this agent produced relatively little weight loss in patients with refractory obesity when compared with placebo or phenmetrazine hydrochloride.[78] In another trial, Enzi and colleagues reported that mucilage may be an effective agent.[79] Of 28 patients recruited, 16 completed a double-blind crossover trial of 30 days each. During the second 30-day period following the crossover, the group receiving the mucilage lost significantly more weight than those on diet alone. Fiber may enhance weight loss by restricting energy intake and aiding compliance in adhering to a diet. Three recent studies showed that obese patients treated with added fiber lost 1.4 to 2.1 kg (3 to 5 lb) more than the placebo-treated patients in trials lasting 8 to 12 weeks.[80] Thus, fiber may have some value in treating obesity.

Sucrose polyester. Sucrose polyester (Olestra) is an indigestible fat produced by esterifying sucrose with fatty acids of appropriate length to give it the characteristics of normal cooking oil. Adding this agent to the diet will reduce the absorption of cholesterol and vitamin A by 67% and 42%, respectively. Clinical trials with this substance showed that overweight subjects lost weight.[81] In these studies, subjects were fed a diet consisting of basal foods plus snacks that included potato chips, bagels, fruit, soda, cookies, vegetables, and pretzels. The snack consumption was limited to an amount equal to 60% of the baseline meals. During one period, sucrose polyester was substituted in the diet, replacing 40 grams of fat per 1,200 kcal of diet. The principal variable in this experimental setting was the consumption of snacks. During the period when sucrose polyester replaced fat in the diet, there was no significant difference in the number of snacks consumed. The total energy intake during meals was significantly reduced, however, from 1,801 kcal during the placebo period to 1,270 kcal during the period of substitution with sucrose polyester. Thus, there was no apparent increase in the intake of snacks when the nonabsorbable sucrose polyester replaced fat in the diet. A subsequent study by Mellies and co-workers, however, failed to show any significant effect of substituting sucrose polyester for fat in the diet of five obese subjects.[82] The reasons for the reduction in caloric intake in the study by Glueck and colleagues and the failure to detect a reduction in the second study remain unexplained.[81]

Human Chorionic Gonadotropin

The treatment of obesity with diet and injections of human chorionic gonadotropin has been in use for more than 30 years. The rationale for this drug was the observation that in persons with pituitary obesity, injections of this drug were associated with weight loss. Over the past ten years, there have been three double-blind, placebo-controlled parallel studies comparing injections of chorionic gonadotropin and placebo added to a very-low-calorie diet.[83-85] In no instance was there a statistically significant enhancement in the rate of weight loss during treatment with chorionic gonadotropin when compared with receiving placebo.

Invasive Treatment of Obesity

Gastric Bubble

Two different gastric bubbles have been developed. The first, developed in Europe, is known as the Ballobos bubble.[86] Clinical trials with this balloon are currently under way in a number of countries. In the United States, the Garren-Edwards bubble has been most widely used, with as many as 20,000 being inserted between 1985 and 1986 costing $2 to $4 million. The rationale for this procedure is that placing a distended object in the stomach will cause smaller quantities of food to be eaten. In controlled trials comparing the use of the gastric bubble to sham insertions, there was no evidence that the balloon is more effective than the diet with which it is associated.[87]

Jaw Wiring

Mandibular fixation, more popularly called jaw wiring, has been used to reduce the intake of solid foods in overweight patients. Several clinical trials have shown that persons with their jaws wired lose weight steadily while the jaws remain wired. In one study of 17 patients, 2 dropped out in less than a month.[88] The median weight loss at six months was 25.3 kg (52 lb), which is comparable to that from other more drastic operative procedures. Following removal of the wires, however, two thirds of the patients regained some or all of their weight. Recently Björvell and associates reported that two years following mandibular fixation, women maintained a 13.8-kg (30-lb) loss compared with a maximum loss of 19 kg (42 lb) at the time wires were removed.[89] To improve the long-term results, Garrow and Gardiner have introduced an abdominal nylon cord that at the end of the weight-loss period is attached around the abdomen.[90] According to their reports, this has improved the long-term maintenance of weight loss following mandibular fixation.

Vagotomy

The vagus nerve controls gastric emptying and a variety of other gastrointestinal and hepatic functions. Between 1977 and 1979, Kral and Gortz did bilateral truncal vagotomy without gastric drainage in 11 women and 2 men who were morbidly obese.[91] The mean weight loss was 18.2 kg (40 lb), with a range of 2 to 24 kg (4 to 53 lb). A second small series was reported in 1981, but these patients had problems with gastric emptying due to vagotomy. The use of vagotomy in one patient with the Prader-Willi syndrome and in one patient with hypothalamic obesity was of limited success. Recently Kral has coupled vagotomy with gastroplasty and suggests that this may improve the effectiveness of the gastric operation as a treatment of morbid obesity.[92]

Liposuction or Suction-Assisted Lipectomy

Local fat deposits can be altered cosmetically by liposuction, an operative procedure developed in the past ten years.[93] It can be done under local anesthesia, and published pictures suggest that it is a promising technique for contouring or molding small to modest amounts of fat. Both wet and dry suction lipectomy procedures have been developed. The difference depends on the quantity of fluid injected before aspiration. An incision 1 to 2 cm long is made, usually in a region covered by clothing. The suction probe is fanned out from this incision site and honeycombed by inserting the cannula with its open face down, which then aspirates tissue. As much as 2.5 kg (5 lb) has been aspirated at one time, but when the quantity exceeds 1 kg, patients usually require fluid replacement because of blood loss. Successful operations have usually been done on younger persons with limited quantities of fat to be removed, where the underlying elastic properties of the skin are sufficient to allow tightening over the aspirated areas. Difficulties such as dimpling or a wavy contour have been observed, and seromas and infections have also occurred.

Gastrointestinal Procedures

Various surgical methods have been used to decrease the quantity of food entering the gastrointestinal tract or its duration of retention in that system. These include esophageal banding, gastric bypass with various kinds of diversion from the small upper pouch, gastroplasties including the vertically banded gastroplasty, and jejunoileal bypass operations (Figure 6).

There is little doubt that weight loss can be substantial with all of these procedures. Guidelines for the use of these operations have been published.[94]

Gastric operations. The idea of reducing the gastric pouch size as an approach to obesity was introduced by Mason and Ito in 1967.[95] Since that time, various procedures have been developed (Figure 6). At one end of the spectrum are banding procedures, which have been used on both the esophagus and stomach. At the other end of the spectrum are the gastrointestinal anastomoses in which the antrum and fundus of the stomach are anatomically or functionally separated and the fundal pouch drained into the intestine through a loop enterostomy or a Roux-en-Y anastomosis. We will refer to this group of operations as gastrointestinal bypass. The other group of operations narrows the connection between the fundus and antrum but leaves them intact. These include wrapping procedures, transverse gastric banding procedures, and vertical banding procedures. The number of operative procedures now available raises some concern about whether the most desirable procedure has yet been identified. This concern was expressed by Freeman and Burchett as follows: "Despite 12 years of experience with gastric operations for morbid obesity in the surgical literature, the ideal technique remains unknown."[96]

The mechanism for weight loss with all of the gastric operations appears to be reducing food intake. The distribution of calories between carbohydrates, protein, and fat does not change, but the frequency of eating is increased in most patients.

Several good trials exist comparing gastrointestinal bypass with gastroplasty. In general, patients with gastric (antral) bypass lose more weight than those with gastroplasty. Pories and co-workers reported a prospective, randomized trial comparing the results in 42 patients who had gastric (antral) bypass with those in 45 patients who had a gastroplasty.[97] Patients for whom the gastric bypass was done lost 15% more weight at 12 months and 24% more weight at 18 months than those with gastroplasty. There were no technical failures in the gastric (antral) bypass group, but 28 of the 45 operations using gastroplasty were counted as failures. Sugerman and colleagues have recently provided some insight into this difference.[98] They divided patients into sweets

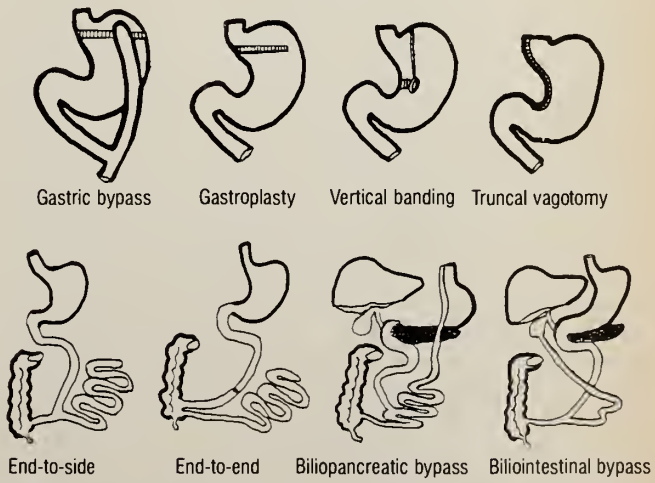

Figure 6.—Operative treatments for obesity are shown schematically.

eaters—defined as those who ate 300 kcal of sweets at least three times a week—and non-sweets eaters. The difference in the rate of weight loss between patients with gastroplasty and those with gastric-antral bypass (Roux-en-Y) was among the sweets eaters. Among the non-sweets eaters, there was no difference in the rate of weight loss between these two operations. This suggests that a dietary history of eating sweets frequently would lead to the selection of a gastric bypass.

Complications associated with gastric operations can be summarized in several categories. First are the operative problems (Table 5).[99] Operative mortality is usually less than 1%. Problems with anastomotic connections can require reoperations. Other perioperative difficulties are within reasonable bounds. Though weight loss with gastroplasty is substantial, failure rates as high as 50% have been reported when all reversals, revisions, and patients lost to follow-up are considered.[100] The third group of complications are the result of the changes and include anemia due to iron and vitamin B_{12} deficiency, as well as thiamine deficiency and its associated neuropathy.

These operations also have advantages, the most obvious of which is substantial weight loss. Another advantage of operative intervention is an improvement in the quality of life. In one series 10 of 44 patients had returned to school and another 10 had reported a change in their occupation. Patients' self-concepts improved after the operation, and there were fewer reports of feeling angry. Patients tended to feel more attractive, calmer, and less depressed. Of 44 patients, 41 were definitely glad that they had had the operation, and 19 (43%) spontaneously said that the operation was the best thing that ever happened to them.[101]

In summary, though both gastric bypass and gastroplasty procedures produce large amounts of weight loss, long-term results appear to more consistently occur with the gastric bypass operation.

Jejunoileal operations. Four variants of the jejunoileal bypass have been used (Figure 6). The two most widely studied are the end-to-side and the end-to-end operations. In comparative trials with gastric and jejunoileal bypass operations, several groups of workers have all reported similar rates of weight loss.[102-104] There is, however, a higher frequency of metabolic complications following the jejunoileal bypass, leading almost all surgeons to abandon its use. The wide variety of metabolic difficulties associated with this procedure include diarrhea, electrolyte imbalance with hypokalemia and hypocalcemia, bacterial overgrowth of the intestine associated with deconjugation of bile acids and bile-induced diarrhea, liver failure, and circulating immune complexes associated with bacterial overgrowth.

The mechanism of weight loss associated with the jejunoileal bypass appears to be similar to that of the gastric bypass and involves a substantial decrease in food intake.

Two additional operative procedures have been developed that are currently being explored. The first of these is the biliointestinal operation,[105] in which the defunctionalized loop of ileum is attached to the gallbladder, thus allowing drainage of the large bile flow. This provides a volume of flow through the defunctionalized loop and allows the enterohepatic circulation for bile salts to remain intact. The bile acid-induced diarrhea and bacterial overgrowth are notably reduced. One limitation of this procedure is that an intact

TABLE 5.—*Comparison of Bypass Operations for Obesity**

Result	*Bypass Operation*	
	Jejunoileal	*Gastric*
Mortality (early), %	0-11.5	1.4
Vomiting	Rare	Common
Diarrhea	Common	Rare
Electrolyte depletion	Common	Rare
Peptic ulceration, %	Rare	1-2
Liver failure, %†	5	0
Urinary calculi, %†	1-32	1
Osteomalacia, %†	17-48	??
Revision due to inadequate weight loss, %	5-20	10-40
Reversal due to complications, %	1-23	1
Follow-up, yr	26	11

*Adapted from Joffe.[99]
†Late complications.

TABLE 6.—*Overall Assessment of Risk, Cost, and Efficacy of Treatments of Obesity*

Treatment	*Rate of Weight Loss Compared to Control**	*Risk of Treatment*	*Cost of Treatment*	*Long-term Efficacy*
Conventional diet	+	Low	$-$$	Low
Very-low-calorie diet	++	Moderate	$$-$$$	Low to moderate
Starvation	++	High	$-$$$$	Low
Behavior modification	+	Low	$-$$	Moderate
Work-site programs	±	Low	$	Low
Self-help groups	+	Low	$	Low to moderate
Psychoanalysis	+	Low	$$$	Low to moderate
Hypnosis	±	Low	$$	Low
Exercise	±	Low to moderate	$-$$	Low to moderate
Appetite suppressants	+	Low to moderate	$-$$	Low
Human chorionic gonadotropin	0	Low to moderate	$$	Low
Fiber (bulk)	±	Low	$	Low
Gastric bubble	±	Moderate	$$$	Low
Jaw wiring	+	Low to moderate	$$	Low
Suction lipectomy	±	Moderate	$$$	Moderate
Gastric bypass	++	High	$$$$	High
Gastroplasty	++	High	$$$$	High
Jejunoileal bypass	++	High	$$$$	High
Scopinaro procedures	++	High	$$$$	High

*0=none compared with vehicle, ±=very slow, +=slow, ++=fast.

gallbladder is essential, and with the high frequency of cholelithiasis in obese patients, the gallbladder is often absent.

The second operation, the biliopancreatic procedure, was developed by Scopinaro and associates.[106] In this operation, the gastrointestinal circuit at the stomach is divided into two conduits, one draining the fundal portion of the stomach into a long segment of intestine that at a distal point is connected to the drainage from the antrum, pancreas, and bile ducts. Thus, adequate flow remains through the biliary tree and through the duodenojejunal segment, and anastomosis of these two loops can occur at a point determined by the surgeon. Weight losses with this operation have been entirely satisfactory, with a suggestion of decreased long-term complications.[107] This operation is technically more difficult than other procedures described, however.

Summary and Conclusion

The rate of weight loss varies substantially among treatments (Table 6). Surgical treatment including gastroplasty or gastric bypass, starvation, and very-low-calorie diets produce the most rapid weight loss. Intermediate rates are seen with conventional diets, appetite-suppressing drugs, and behavior modification. The least rapid rate of weight loss is seen with exercise alone.

For most treatments, safety is the inverse of the rate of weight loss. Although an operation clearly carries the highest risk, gout, cholelithiasis, and death have been reported during treatment with starvation and very-low-caloric dieting. Conventional diets and behavior modification are the lowest risk treatments, but exercise and appetite-suppressing drugs also carry little risk.

Among treatments, surgical manipulation of the gastrointestinal tract has the best long-term outlook, albeit there are a substantial number of patients who regain weight and

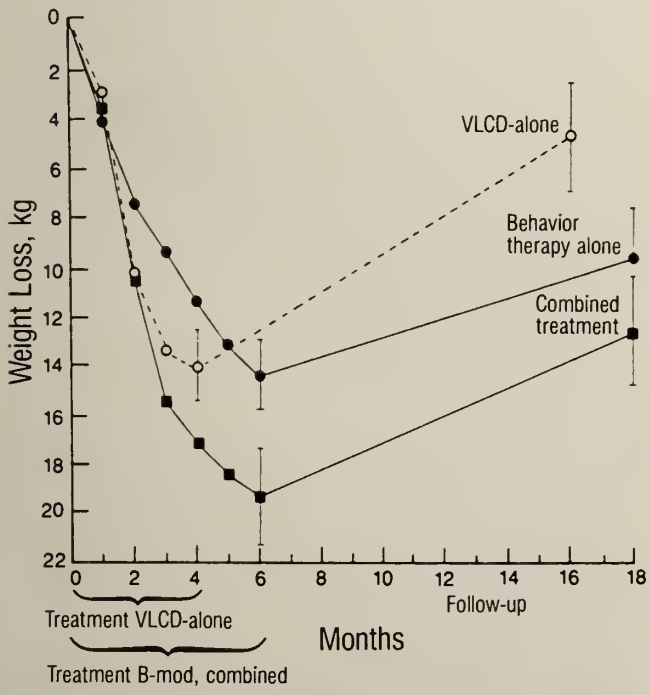

Figure 7.—Very-low-calorie diets (VLCD) and behavior modification (B-mod) are compared. The treatment program of 4 to 6 months included very-low-calorie diets, behavior therapy, or a combination. After follow-up of 12 to 14 months, the groups receiving behavioral therapy did better than those treated with very-low-calorie diet alone (from Stunkard[107]).

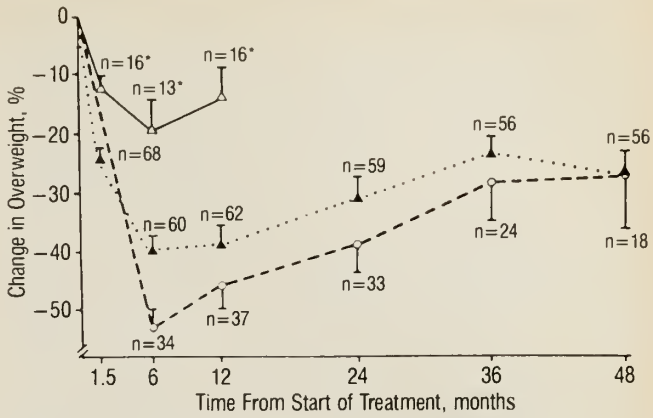

Figure 8.—The chart shows long-term follow-up after weight loss (from Björvell and Rössner[109]). △ = control patients, ▲ = patients who underwent behavior modification, ○ = patients who underwent jaw wiring for 6 months, $^*P<.001$

many others who require reoperation. Among the noninvasive treatments, good long-term comparative studies are few. We will review them to indicate the central place of behavior modification and nutrition education.

In a five-year follow-up of patients treated with behavior modification or nutritional advice in a physician's office, Stunkard showed an initial result that favored behavior modification.[108] After five years, however, the two treatments were essentially identical. Although several studies have compared pharmacologic treatment and behavior modification in the short term, only a few provide longer term follow-up. In one of them, patients treated with fenfluramine fared better during the six months of treatment. Over the next 12 months, however, the regain of weight by the drug-treated patients was greater than by those receiving behavior modification, with a net preference for behavior modification.

Although rates of weight loss with very-low-calorie diets are among the most rapid, long-term maintenance of weight loss appears to be no better than with behavior modification (Figure 7).[108]

Finally, jaw wiring and behavior modification have been compared over a four-year period (Figure 8). The maximal weight loss was greatest in those whose jaws were wired. After four years, with a high level of follow-up, the behavior treatment group and formerly jaw-wired patients receiving behavior modification treatment both maintained a reduction of 30% of their initial overweight.

Even with the excellent long-term results with surgical treatments, it seems clear that behavior modification is a key element of long-term success with weight loss. This may be because patients are continuing to be treated. As noted earlier, the treatment of obesity has many similarities with the treatment of other chronic diseases. Pharmacologic agents can control hypertension in most patients, but few if any physicians would expect hypertension to remain under control if drug therapy were discontinued. So with obesity, it is unrealistic and unreasonable to expect patients who lose weight to remain thinner when their treatment is terminated. Thus, behavior modification and a regular exercise program are essential continuing treatments that are necessary if people who lose weight are to remain thinner.

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Specialty Conference

Cardiac Transplantation

Selection, Immunosuppression, and Survival

Discussants
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BARRY D. KAHAN, MD, PhD; *and* DAVIS C. DRINKWATER, MD

An edited summary of an interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

Cardiac transplantation has evolved from an experiment to an accepted therapy for severe heart failure. Increasing competition for donor organs mandates a greater emphasis on selection and timing for transplantation and paradoxically forces more reliance on aggressive medical therapy for all patients after evaluation. The growth of recipient and donor pools may enhance the opportunity for assessing histocompatibility, for which distinguishing between autoantibodies and human leukocyte antigen-determined reactivity is important, and some general nonresponders may be detected. Therapy with cyclosporine has improved the outcome after transplantation, but further refinement is needed, perhaps with pharmacologic synergy, to minimize nephrotoxicity and maximize specific immunosuppression. Survival is more than 80% at 1 year, after which the incidence of acute rejection and infection declines and accelerated atherosclerosis becomes prominent. Although resuming employment is not always possible, the overall quality of life is excellent after cardiac transplantation.

(Stevenson LW, Laks H, Terasaki PI, et al: Cardiac transplantation—Selection, immunosuppression, and survival [Specialty Conference]. West J Med 1988 Nov; 149:572-582)

LYNNE WARNER STEVENSON, MD*: Cardiac transplantation has slowly evolved from an experiment to an accepted therapy for end-stage heart disease. In 1905 Carrel and Guthrie reported transplanting a heart into the neck of a dog.[1] Mann and associates later showed functioning of a transplanted heart for four days before rejection occurred.[2] The elucidation of the graft rejection response by Lance and Medawar contributed to the design of immunosuppressive therapy[3] and ultimately to successful human renal transplantation.[4] Lower and Shumway pioneered the surgical technique and immunosuppressive regimen[5] that permitted the first human cardiac transplantation to be done in 1966 in Capetown.[6] After the initial enthusiam led to widespread failure of the procedure,[7] Shumway persevered and ultimately proved the clinical value of the technique, which by 1981 was yielding a 63% one-year survival.[8] The introduction of cyclosporine in 1981 has further improved the results of transplantation.[9] After an exhaustive review of the Battelle report,[10] cardiac transplantation has been federally approved as the best therapy for eligible patients.

With the acceptance of cardiac transplantation, the numbers of transplant centers and accepted candidates are increasing the strain on the already limited donor supply.[11] Attention must be directed to the selection for and timing of transplantation. Donor procurement and matching must be increasingly efficient. An increased understanding of tissue antigenicity and improved diagnosis and therapy for immunosuppression will be necessary to maximize graft acceptance and minimize complications.

Selecting and Treating Patients Referred for Transplantation

When heart transplantation was in its experimental stage, recipient selection was not a major problem. For an experiment, patients were not eligible until they were overtly moribund.[12] On the other hand, any potential contraindication could be rigidly applied. For a life-saving procedure, however, that is now considered standard therapy but is limited by scarce resources, selection and timing become critical issues.

Many patients with severe heart disease are not candidates for transplantation. Even among patients passing the initial screening in an outpatient clinic, fewer than half are placed on the waiting list after a full in-hospital evaluation (Table 1).

The first question that arises during the evaluation of a possible candidate for transplantation is whether the heart is sufficiently diseased to warrant replacement. As more than 95% of the patients are referred because of dilated ventricular failure, the medical history of this disease should determine when transplantation is indicated. The original criteria for transplantation included New York Heart Association class IV symptoms. Increasingly more patients are being

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ABBREVIATIONS USED IN TEXT

DTT = dithiothreitol
HLA = human leukocyte antigen
Ig = immunoglobulin

referred earlier in the course of their disease, however. To investigate whether any of these patients should be considered for transplantation, survival was determined retrospectively for a group of 28 patients who, during evaluation at UCLA or the Stanford University Medical Center, were considered to be too well for transplantation. All patients had idiopathic cardiomyopathy and ejection fractions of less than 30%. Only half of the patients survived a year without transplantation, with 82% of the deaths occurring suddenly.[13] A history of ventricular arrhythmias was strongly predictive of subsequent sudden death, whereas a stroke volume of less than 40 ml per beat was predictive of eventual circulatory failure. Neither subsequent antiarrhythmic nor vasodilator therapy correlated with the outcome, but the regimens were designed empirically by the referring physicians and were not standardized by a rigorous demonstration of clinical efficacy. We have found that most patients referred even with severe symptoms of chronic heart failure can achieve a reasonable level of function on therapy tailored specifically to hemodynamic goals,[14] but they also remain at a high risk for sudden death. Thus, we currently consider for transplantation not only patients with severe symptoms of heart failure but also those with limited symptoms who are felt to be at a particularly high risk. The same study also showed that ventricular function improved significantly during follow-up in 20% of patients, all of whom had a symptom duration of seven months or less at the time of presentation. Thus, for patients with a short symptom duration who do not appear to have an unusually high risk, it may be particularly important to defer transplantation.

Once patients have been discerned to have cardiac disease severe enough to warrant transplantation, they must be evaluated for other conditions that would limit the likelihood of a good outcome after the procedure. In general, a patient must not have any noncardiac disease that would itself shorten life expectancy or increase the risk of complications (Table 2). The specific criteria are undergoing perpetual remodeling from those originally prepared for the transplantation experiment.[15] Most limits have been pushed in our own program (Table 3) and in others. The most obvious limit is age, which was originally 40, then was extended to 55. Carrier and co-workers have shown that carefully selected patients older than 50 do well.[16] Such patients, however, who often have many other problems, must be selected with particular care.

TABLE 1.—*Results of Full Evaluation for Cardiac Transplantation, UCLA, 1984-1987*

Patients Evaluated, N=250	*Number*
Accepted	110
Died during evaluation	5
Rejected	90
Physical contraindications	70
Noncompliance	20
Deferred	45
Recent disease onset	15
No prior medical therapy	10
Patient refusal	20

Fixed pulmonary hypertension can lead to fatal right heart overload in a newly transplanted heart but may not be distinguishable from reversible pulmonary hypertension without extensive pharmacologic trials. Renal and hepatic function are also profoundly influenced by the degree of circulatory compromise and may not meet criteria standards until after days of hemodynamic optimizing therapy.

After transplantation, patients need to take 12 to 25 doses of medicine daily and submit to 15 to 25 biopsies in the first year. A history of medical compliance and emotional stability are crucial for a good long-term outcome. Even patients without a history of noncompliance or depression may respond to fluctuating steroid dosages and repeated complications by stopping immunosuppressive therapy in a passive suicide attempt. Of four deaths from acute rejection, three were caused by noncompliance. Most patients showing noncompliance were previously predicted to be at some risk. Two patients, however, were accepted into our program after being refused elsewhere on psychosocial criteria and are currently alive after 18 months, although some of the anticipated problems have arisen.[15] The existence of strong family support is important for compliance and outcome but in most programs is no longer essential for acceptance. The active

TABLE 2.—*UCLA Standard Criteria for Heart Transplantation*

Indications
- Severe heart disease despite adequate medical therapy
  - Unacceptable quality of life because of disabling symptoms of congestive heart failure
  - *or*
  - Unacceptable risk of cardiac death within the next year, despite limited symptoms of congestive heart failure
- No other reasonable surgical option

General Eligibility
- The patient must not have any noncardiac condition that would in itself shorten life expectancy or increase the risk of death from rejection or from complications of immunosuppression, particularly infection

Specific Contraindications
- Age older than 65; age older than 55 is a relative contraindication
- Active infection
- Active ulcer disease
- Severe diabetes mellitus
- Severe peripheral vascular disease
- Limited pulmonary function* or history of chronic bronchitis
  - Forced expiratory volume in 1 s, forced vital capacity, or single breath diffusion capacity for carbon monoxide less than 60% predicted is absolute contraindication; less impairment is relative contraindication
- Creatinine > 2 mg/dl; creatinine clearance < 50 ml/min*
- Bilirubin > 2.5 mg/dl, serum aspartate aminotransferase > double normal, prothrombin time > 14 s off warfarin sodium therapy*
- Pulmonary artery systolic pressure > 60 mm of mercury*
- Mean transpulmonary gradient > 15 mm of mercury*
- High risk of life-threatening noncompliance
  - Inability to make strong consistent commitment to transplantation program
  - Cognitive impairment severe enough to limit comprehension of medical regimen
  - Psychiatric instability severe enough to jeopardize incentive for adhering to long-term medical regimen
  - History of alcohol or drug abuse
  - Failure to establish stable address or telephone number
  - Previous demonstration of repeated noncompliance with medication or follow-up

*May need to provide optimal hemodynamics by administering sodium nitroprusside, dobutamine hydrochloride, or both for 72 hours to determine reversibility of organ dysfunction caused by heart failure.

participation of a psychiatrist and a social worker with the transplant team is essential for the thorough evaluation of these patients and for continued psychosocial risk assessment and modification after transplantation.

Although the general criteria for evaluating candidates are relatively uniform, there are currently no guidelines as to the urgency with which transplantation should proceed once a patient has been accepted. In our program, 15% of patients have died waiting for a transplant, which is comparable with that of other large programs.[17] Most of these deaths have occurred suddenly in patients at home awaiting transplantation. With the current donor shortage, waiting periods will increase and the issue of assigning priority status will become more important.[11] The priority status should be adjusted according to the degree of outpatient jeopardy,[17] but the current priority scale has only one outpatient grade.

Priority is frequently given to patients considered so refractory to medical therapy that they cannot be discharged from hospital on oral therapy. A patient should not, however, be deemed refractory on the basis of oral therapy adjusted empirically by a clinical evaluation. Of 40 patients transferred to UCLA from other hospitals where they were considered to have refractory heart failure amenable only to urgent transplantation, 32 (80%) could be discharged home on oral therapy.[18] Despite the apparent failure of previous vasodilator therapy, such patients benefited from titration with the intravenous administration of sodium nitroprusside and diuretics tailored to achieve specific goals that could subsequently be met with high doses of oral vasodilators and diuretics. For severe dilated ventricular failure, the goals are a pulmonary wedge pressure of 15 mm of mercury or less and a systemic vascular resistance of 1,200 dynes $\cdot$ s $\cdot$ cm^{-5} or less,[14] during which the cardiac output is frequently maximal due to the concomitant reduction in regurgitant flow through the secondarily incompetent mitral valve.[19] Maintaining a low filling pressure also decreases the venous congestion that limits these patients and contributes to an increased risk of perioperative complications.

There is a small subset of patients for whom cardiac transplantation must be done urgently, if it is to be done at all. Frequently, truly urgent candidates are those who have acute massive infarction or who cannot be weaned from cardiopulmonary bypass. Urgent priority candidates cannot always be screened as thoroughly as elective candidates and may also be at a higher risk of subsequent complications due to prolonged circulatory compromise. Survival after urgent priority transplantation in 1985 to 1986 for patients of western regional centers was 88% at one month and 80% overall.[18] These results are outstanding for such a sick population but represent an early mortality twice as high as that in the regular priority patients. With the competition for donor organs, an increasing proportion may be diverted to urgent transplantation, with potential compromise of the continued success of cardiac transplantation.

There are currently more than 80 hospitals doing cardiac transplantation in the United States (Figure 1). The evaluation and treatment of patients referred with severe heart failure constitute major responsibilities for any institution committed to cardiac transplantation. Selection and the timing of transplantation should be designed to maximize the years of life gained for each heart transplanted. In addition, the success of transplantation has created a donor shortage that paradoxically forces a greater reliance on medical therapy to allow patients to live comfortably at home until appropriate donors become available.

Histocompatibility Considerations in Heart Transplantation

Human Leukocyte Antigen Matching

PAUL TERASAKI, PhD*: At individual centers, there are only a limited few prospective heart transplant patients. When these few patients are grouped into those with different ABO blood types and different physical sizes, generally little can be done to provide human leukocyte antigen (HLA)-matched donor organs. It is difficult to increase the waiting pool by pooling patients in extended geographic regions because the methods for preserving hearts do not permit long-term storage. Thus, because of the small pool of waiting recipients available for any given donor and the respective storage time, it is practically impossible to do heart transplantation with good HLA matches.

In a retrospective study, Yacoub and colleagues reported that there was a higher survival rate when one HLA-DR antigen was mismatched than when two HLA-DR antigens were mismatched.[21] If these differences can be confirmed, it still may be possible to select donors and recipients on the basis of DR antigen matching. The polymorphism in the DR locus is less than in the HLA-A and -B loci, making it easier

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TABLE 3.—*Transplantation Beyond Standard Criteria*

Contraindications	*Patients, Number*	*Outcome*
Age > 60 yr	10	Postoperative death, 2: death at 4 mo from infection, 1; normal course, 7
Creatinine > 3.0 mg/dl	5	Postoperative death, 2; ongoing hemodialysis, 1; cyclosporine nephrotoxicity, 2
Acute hepatic failure	3	Normal hepatic function, 3
Chronic hepatic failure	1	Chronic hepatic failure, 1
Glucose intolerance	7	Insulin-requiring diabetes, 6*
Heavy smoking history	12	Recurrent bronchitis, 7
Pulmonary asbestosis	1	Recurrent pneumonia contributing to death, 1
Thrombocytopenia	2	Postoperative pericardial tamponade, 1
Marfan's syndrome	1	Aortic dissection at 2 mo; alive and well at 8 mo
Recklinghausen's neurofibromatosis	1	Normal course
Jehovah's Witness	1	Normal course, without transfusion
Noncompliance history	5	Recurrent severe rejection with death at 20 and 23 mo, 2; persistent noncompliance, 3

*One patient died of mucormycosis and lymphoma.

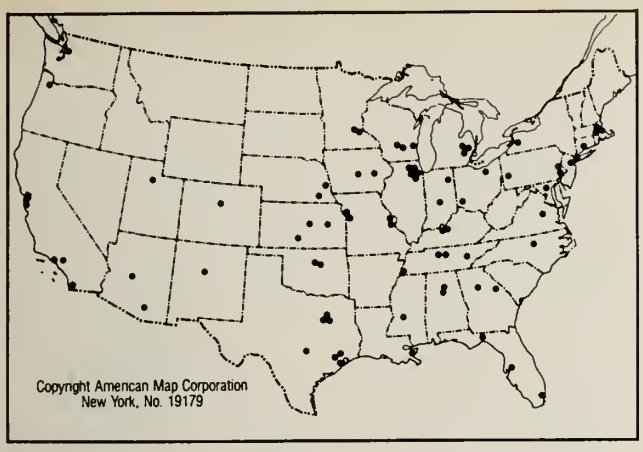

Figure 1.—The map shows the major cardiac transplantation programs in the United States (from Stevenson and Perloff[20]).

to match for the DR locus. Thus, though complete matching may not be possible, matching for certain HLA antigens may become practicable.

Presensitization Screening

All waiting patients should be tested for preformed cytotoxic antibodies to HLA against a test panel of cells from at least 50 randomly selected persons. The standard microlymphocytotoxicity test should be used, preferably with T cells as targets. As a reference, testing against B lymphocytes can also be done. It is important to test patients with dithiothreitol (DTT)-treated serum to establish that the reactions obtained are produced by immunoglobulin (Ig) G antibodies.

In the standard microlymphocytotoxicity test, target lymphocytes can be killed by non-HLA antibodies. Such antibodies are usually autoantibodies that are IgM in nature and react more strongly at 5°C than at 37°C. They occur in various disease states.[22] They even occur in pregnant women and in a small fraction of healthy people.[23] Their exact role is not known, although it has been postulated that they could act as immunoregulatory antibodies.[24] These autoantibodies do not seem to influence the long-term outcome of the transplant or to produce hyperacute rejection.[25]

The specific crossmatching test results available just before transplantation can be confirmed by referring to the previous panel screening test results. A negative crossmatch test in a patient who did not have antibodies to the panel can be readily accepted. A positive crossmatch test in a person shown to be negative on the panel is likely to be a false-positive crossmatch and should be reexamined. It is also helpful to know in advance what frequency of positive crossmatches one would expect for each patient.

Specific Crossmatch Test

Although there have been some reports of successful heart transplants across a positive crossmatching test,[26] it seems that transplants cannot be regularly done across a positive test. We are aware of one definite hyperacute graft failure occurring elsewhere as a consequence of a positive crossmatch. Some of the reported positive crossmatches that have succeeded may have been across a positive auto-T-cell crossmatch test. At UCLA, one patient with a positive crossmatch test had autoantibodies. Once the autoantibodies were inactivated by DTT, the crossmatch reactions were negative. A subsequent heart transplantation in this patient resulted in a successful graft in which there has been no rejection for the first 12 months. It is thus important to establish that the antibody reaction is not a reaction against autoantigens, as described above for the screening test, but is actually against HLA-A and -B loci antigens. The simplest method has been, again, the use of DTT to treat serum. This does not completely guarantee that the antibody is not against HLA, as it principally distinguishes between IgM and IgG antibodies. The HLA antibodies tend to be IgM antibodies. We have thus recommended that crossmatching be done with DTT if a patient's serum has previously been shown to contain IgM antibodies.

In the case of kidney transplants, we have seen some kidney transplants that never recovered function, despite a negative crossmatch between donor and recipient. This phenomenon occurs more often in sensitized patients and patients who have been regrafted than in nonsensitized patients or those with their first transplant. To detect low levels of sensitization, Garovoy and colleagues and others have been studying the use of flow cytometry as a means of doing a more sensitive crossmatching test.[27]

In our experience of 231 renal transplants tested, if the flow-cytometry crossmatch test was negative, the one-month nonfunction rate was 8% compared with 33% if the flow-cytometry crossmatch was positive. This means that among patients who have standard negative crossmatching tests, a positive flow-cytometry crossmatch is predictive of nonfunction for a month in 33% of the transplants, whereas this phenomenon normally occurs in 8% of those judged to have a negative flow-cytometry crossmatch.

Even with a positive flow-cytometry crossmatching test, 67% of the kidneys function within the first month. Thus, there is no absolute contraindication for transplantation by flow cytometry. The rate of nonfunctioning kidneys, however, is much higher in patients with a positive flow-cytometry crossmatch than with a negative flow-cytometry crossmatch. With heart transplantation, when it is critical to have an organ function immediately, it may be more important to use flow cytometry as a crossmatching method.

From the kidney transplant experience, the flow-cytometry crossmatching test should be used in patients who have cytotoxic antibodies or who have had cytotoxic antibodies against a panel of cells. It is less useful in patients who have never had preformed antibodies. Flow cytometry is most valuable in patients who are being regrafted. Fortunately, in heart transplantation the regraft rate is low. As more transplants are done, a greater need for second transplants will arise and the flow-cytometry crossmatch may be more commonly used.

In Vitro Responsiveness Concept

We have been working on the concept that about half of the transplant patients are nonresponsive and can be transplanted with organs from essentially any HLA-incompatible donor. The other half are responders and should receive hearts from donors who have antigens against which the recipient is specifically nonresponsive. Preformed cytotoxic antibodies serve to warn us of specificities against which the recipient will respond. In vitro tests are being developed to predict which specificities would be acceptable and which would not be by any recipients. With these tests, knowledge of antigenicity and responsiveness may be applied to improve the acceptance of a transplanted heart.

Immunosuppression With Cyclosporine

BARRY D. KAHAN, MD, PhD*: Clinical immunosuppressive therapy for cardiac transplantation has improved substantially since the introduction of cyclosporine, a fungal cyclic endecapeptide of novel chemical structure.[28] The previously used immunosuppressive combination of azathioprine, a competitive inhibitor of nucleic acid biosynthesis, and corticosteroids such as prednisone, although manipulated with exquisite attention to detail, had been limited by a narrow therapeutic index. The use of azathioprine and corticosteroids causes a severe depression of the proliferation of nonspecific host immune elements, namely polymorphonuclear leukocytes and monocytes or macrophages, leading to infection with various pathogens, including not only those normally controlled by T cells—viruses, fungi, and protozoa—but also those subject to nonspecific resistance and humoral antibody B-cell-producing bacteria. As a result of the low therapeutic index of the azathioprine-prednisone combination, rejection prophylaxis was rarely achieved and high-dose steroid therapy or antilymphocyte serum, or both, were frequently required for additional immunosuppression. Antilymphocyte serum treatment resulted in further depressing T-cell elements with a frequent occurrence of cytomegalovirus infection and a further reduction in the number of circulating granulocytes.

The initial use of cyclosporine for heart transplantation in the United States at Stanford[29] in 1981 was followed the next year at the Texas Heart Institute (Houston)[30] and at the University of Pittsburgh.[31] From the initial experience, it became apparent that the use of cyclosporine in conjunction with the immunosuppressive regimen previously used resulted in a high risk of lymphomas; many patients had a much more benign, rejection-free posttransplant course than was ever observed using previous immunosuppressive regimens; cyclosporine therapy masks early clinical signs of allograft rejection—namely, fever, atrial arrhythmia, and congestive heart failure—increasing the dependence on the endomyocardial biopsy; and the overall result of transplantation using cyclosporine was improved one-year patient survival by 25%, from 50% to at least 75%. Because of the improved efficacy of cyclosporine therapy, cardiac transplantation was readily extended to patients beyond 50 years of age.[32] The safe dose, however, is limited by side effects of which the most dominant is nephrotoxicity. At present the optimal cyclosporine regimen is unclear; the time of initiation, the dosage of drug, and the use of combination therapy with the other immunosuppressive agents to optimize the prophylaxis of allograft rejection continue to be under intensive investigation.

Mechanism of Action

Cyclosporine inhibits various immune responses based on a cell-mediated host resistance, including allograft rejection, contact sensitivity, adjuvant-induced arthritis, and graft-versus-host disease.[28] The drug acts selectively and reversibly on T lymphocytes, tending to spare other cellular elements. It does not inhibit T-cell-deficient nude mice from responding to lipopolysaccharide by T-cell-independent, B-cell antibody production. Cyclosporine has minimal effects on polymorphonuclear leukocytes, macrophages or monocytes, or natural killer cells.[33] Cyclosporine does not delete T-cell precursors but rather inhibits the capacity of lymphocytes, both primed and particularly unprimed cells, to produce lymphokines.[34]

Lymphokines, which serve as growth factors, recruit and activate cellular elements that amplify the immune response. The effect of cyclosporine in inhibiting lymphokine production affects several subpopulations of T cells including T-helper, T-cytotoxic, and T-delayed hypersensitivity cells. Because there is neither a protein store nor constitutive synthesis of lymphokines, their production is exquisitely sensitive to inhibitors. Separate sets of cyclosporine-sensitive T-helper cells may produce interleukin-2, which stimulates the proliferation and differentiation of cytotoxic and helper T cells and interferon-γ, which stimulates macrophages to produce interleukin-1. The second signal accompanies the first signal antigen to stimulate T-helper cell activation[35] on the one hand and B-cell growth factor, on the other hand, which promotes the proliferation of B cells in the T-cell-dependent responses.

The mechanism by which cyclosporine affects lymphocytes is unclear. Although cyclosporine may alter plasma membrane transduction of the activation signal,[36] it seems more likely that after passive entry into the cell by partitioning into the lipid bilayer, cyclosporine inhibits key enzymes in the activation cascades by competitively binding to hydrophobic sites. One site is the calcium-binding protein, calmodulin, which participates in ligand-induced redistribution of specific receptors to produce capping and ligand-cytoskeletal interactions associated with the initiation of lymphocyte activation via microfilaments, microtubules, coated vesicles, and intermediate filaments.[37] A second site is diacylglycerol, which is normally almost absent from membrane but is transiently produced in response to extracellular signals. A third site is protein kinase C, a Ca^{2+}- and phospholipid-dependent enzyme that phosphorylates seryl and threonyl but not tyrosyl residues of many endogenous proteins.[38] Finally, cyclosporine may affect the pathway of inositol phospholipids to effect arachidonic acid metabolism.

There are several alternative hypotheses to the one that postulates cyclosporine binding to hydrophobic domains of cytoplasm critical for activating the lymphocyte response. The inhibition of the cytoplasmic release of selective lymphokine gene depressor substances, or the masking of regulatory genes determining lymphokine expression at the nuclear level, represent two additional mechanisms by which cyclosporine selectively inhibits lymphokine depression. These mechanisms prevent the generation of lymphokine messenger RNA (mRNA), the step in the activation cascade that has been clearly documented to be inhibited by cyclosporine therapy. Although one cannot exclude a direct cyclosporine effect on the processing or transition of mRNA, it seems unlikely that the drug affects pretransitional protein modification or secretion or leads to a rapid destruction of secreted lymphokines. Because the exact site of cyclosporine action is unknown, one cannot presently define the cyclosporine tissue binding site that mediates the inhibition of lymphokine generation.

Clinical Results of Cyclosporine Transplantation

The use of cyclosporine has clearly had an effect on kidney and liver transplantation. It has not only improved the survival of these allografts but also streamlined the process, extending transplantations to high-risk recipients, such as

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elderly patients. Furthermore, the use of cyclosporine has mitigated the need for pretransplant immune conditioning with blood transfusion[39] and probably lessened the impact of HLA tissue typing. These favorable clinical data result from a high immunosuppressive therapeutic index; neither the incidence of infection[40] nor that of malignant lesions is increased with cyclosporine compared with previous regimens in Penn's worldwide registry[41] or in Sheil's Australian experience.[42] For heart transplantation, the overall duration and thereby cost of the initial admission after the surgical procedure were reduced from $91,000 to $52,000 for patients on a combined regimen of cyclosporine and prednisone. Nephrotoxic side effects limit the safe drug dose, however.

Several alternative regimens have been recommended to achieve optimal immunosuppression with minimal toxicity. A single-drug regimen using cyclosporine only, beginning at 25 mg per kg body weight per day, was recommended for renal transplant recipients by Calne and associates[43] because of the high frequency of neoplasms occurring with their previous regimen of the same dose of cyclosporine combined with the usual doses of cyclophosphamide and prednisone. This concern was reinforced by a high incidence of lymphomas when cyclosporine was merely substituted for azathioprine in the Stanford protocol of rabbit antilymphocyte serum and steroids. Because most kidney recipients in the US experience rejection episodes on monodrug therapy, it is almost certainly insufficient for rejection prophylaxis in cardiac transplantation, unless there are substantial refinements to individualize the cyclosporine regimen.

The most widely used double-drug regimen involves cyclosporine and prednisone. For our cyclosporine regimen we use a continuous infusion of 2.5 mg per kg per day to achieve steady-state serum concentrations of 150 ng per ml, as measured by the radioimmunoassay technique, for the first three posttransplant days before oral therapy.[44] For renal transplant recipients the regimen begins at a dose of 14 mg per kg per day, thereafter tapering to 10 mg per kg per day at two weeks and 7 mg per kg per day at two months, guided to keep the serum trough levels at 100 to 250 ng per ml. The steroid regimen begins at 120 mg given orally daily, tapering to 30 mg at day 6 and 20 mg by day 60. In cardiac transplantation, the regimen is modified, using higher cyclosporine doses to maintain serum trough values at 200 to 400 ng per ml. The steroid regimen also begins at 120 mg orally daily but does not reach 20 mg a day until eight months posttransplant. Our one-year patient survival on this regimen was 74% with unrestricted cardiac transplantation of 132 recipients between 6 months and 62 years of age, regardless of transfusion status and without splenectomy. The immunosuppressive therapeutic window was inferior to that noted in renal transplantation; 81% of heart recipients experienced infectious episodes, of which 60% were fatal, and 75% of patients experienced rejection episodes. On an average, patients experienced 1.9 rejection episodes, receiving at least one and generally two courses of high-dose steroids. Steroid-resistant rejections, which occurred in about 40% of our heart recipients, required the intravenous administration of equine antilymphocyte serum or murine OKT3 monoclonal antibody.

A double-drug regimen alternative to cyclosporine and prednisone uses cyclosporine and azathioprine. Yacoub and associates reported 81% one-year and 77% two-year patient survival rates in 188 heart recipients.[21] Because corticosteroid use was restricted to antirejection therapy, the overall morbidity seemed to be reduced.

The early use of cyclosporine-prednisolone immunosuppression at the Stanford University Medical Center led to a high incidence of nephrotoxicity and the need for long-term dialysis therapy in several otherwise successful transplant recipients.[45] This adverse outcome probably resulted from the initial use of high and prolonged cyclosporine doses.[46] To reduce the cyclosporine dose, the Stanford group now uses triple-drug therapy with cyclosporine (8 mg per kg per day), azathioprine (2 to 3 mg per kg per day), and prednisone, a regimen that has reduced the incidence of renal dysfunction and afforded 75% one-year cardiac graft survival. Because of the increased risk of nephrotoxicity in renal allografts during the immediate posttransplant phase, Simmons and co-workers recommended the use of antilymphocyte serum for an initial five- to ten-day postoperative period to spare the newly engrafted kidney from injury.[47] When this approach of an initial four days of antilymphocyte serum-azathioprine-prednisone therapy without cyclosporine was used to avoid early postoperative renal dysfunction after cardiac transplantation, Schüler and colleagues reported decreased patient survival.[48] These workers now advocate beginning cyclosporine therapy at 24 hours rather than 96 hours posttransplant. A quadruple-drug regimen has recently been introduced to intensify the immunosuppression and reduce the incidence of allograft rejection episodes. Cyclosporine in moderate (6 to 8 mg per kg per day) doses is combined with azathioprine (2 to 3 mg per kg per day), usual doses of prednisone, and a five- to ten-day course of antilymphocyte serum.

There are several criticisms of complex immunosuppressive cocktails used in triple- and quadruple-drug regimens. First, there are few well-controlled animal or human data suggesting that the other agents afford additional, let alone synergistic, immunosuppression with cyclosporine. Second, there is no evidence that the immunosuppressive combinations reduce cyclosporine-induced toxicity. The overall rates of graft function and patient survival found at most centers seem similar independent of the drug regimen. Randomized, controlled, prospective trials of cyclosporine-azathioprine-prednisone immunosuppression versus cyclosporine and prednisone failed to document a benefit on renal graft survival for the combined regimen,[49] which may actually increase morbidity and mortality.[50] The benefits of combined regimens for cardiac transplants should be assessed with placebo-controlled, double-blind trials.

Pharmacologic Combination Regimens to Potentiate the Cyclosporine Effect

Various pharmacologic combinations have been advocated to augment the immunosuppressive action or reduce the renal injury of cyclosporine. Because calcium ion is critical to early lymphocyte activation events and because cyclosporine itself has no effect on calcium permeation,[33] calcium channel inhibitors might potentiate cyclosporine immunosuppression. In normal lymphocytes, McMillen and associates found verapamil to potentiate cyclosporine action.[51] Verapamil inhibited the capacity of phorbol myristate acetate to override cyclosporine inhibition of protein kinase C, presumably by interfering with the interaction with adenosine triphosphate. Similarly, Holman and co-workers found amiloride to potentiate the cyclosporine effect,[52] presumably

by blocking adenosine triphosphate availability to protein kinase C.[53] Because the phorbol myristate acetate cannot totally override cyclosporine inhibition, they concluded that cyclosporine probably also inhibits events distal to protein kinase C. The further development of therapeutic agents selectively inhibiting cytoplasmic activation events should yield drugs displaying pharmacologic synergism with cyclosporine.

Another drug possibly synergistic with cyclosporine is the dopamine antagonist, bromocriptine, which blocks pituitary prolactin release. Russell and colleagues suggest that the mechanism of cyclosporine is to inhibit the binding of prolactin to the outer surface of lymphocytes.[54] On antigenic stimulation of normal, untreated lymphocytes, surface prolactin is believed to amplify the immune response of the same and surrounding cells by inducing ornithine decarboxylase, the initial enzyme in the polyamine cascade preceding DNA synthesis.[55] Bromocriptine potentiated the immunosuppressive effect of subtherapeutic amounts of cyclosporine in animal models of graft-versus-host reaction in vivo[56] and S-antigen-induced posterior uveitis in female rats.[57]

Just as pharmacologic agents may potentiate the therapeutic action, so may they mitigate cyclosporine-induced nephrotoxic effects, provided that these actions occur by distinct mechanisms. A major component of renal impairment is reduced blood flow[58] due to a glomerular afferent arteriolar vasoconstriction. After a bolus of cyclosporine was administered to rats, Murray and associates[59] and Moss and co-workers[60] noted a sympathomimetic vasoconstriction, which was ameliorated by renal denervation or by administering dibenzylene or prazosin hydrochloride. Ryffel and colleagues found that ergoloid mesylates (dihydroergotoxine mesylate), a vasodilator with dopaminergic effects that causes central and peripheral α-adrenoreceptor blockade, ameliorated cyclosporine toxicity in spontaneously hypertensive rats.[61] A clinical trial in autoimmune diseases of the eye by Nussenblatt and associates, who administered a daily dosage of 3 mg of cyclosporine,[62] did not confirm the benefit observed with 6 to 8 mg by Benatzen and co-workers.[63] Vincent and colleagues claim that ergoloid benefits renal allograft hemodynamics,[64] but a double-blind, placebo-controlled study by the Canadian Multicenter Group of ergoloid mesylates added to cyclosporine from the time of renal transplantation has not yet shown a clear benefit.

Because cyclosporine-treated renal transplant recipients studied by Bantle and associates displayed a suppressed rather than stimulated renin-angiotensin system,[65] the only other likely mechanism of renal vasoconstriction is an imbalance of eicosanoid products, which regulate cortical blood flow and glomerular function. Cyclosporine might reduce production of the renal cortical vasodilator, prostacyclin, relative to the vasoconstrictor prostanoid, thromboxane. Indomethacin or meclofenamate inhibition of prostaglandin E_2 synthesis is known to increase nephrotoxicity. Although Brown and Neild found that cyclosporine inhibits prostacyclin synthesis by cultured human endothelial cells,[66] other investigators have not found this inhibition at the glomerular level[67,68] or on rat renal cortical slices.[69] Paller and Murray showed cyclosporine administration to increase rat urinary prostacyclin excretion, suggesting an elevated degree of intrarenal synthesis.[70] Adu and co-workers, however, found that prostaglandin excretion decreased in renal allograft patients who received cyclosporine.[71] Previous studies by Makowka and colleagues were inconclusive because the administered prostaglandins also decreased the cyclosporine internal absorption and increased hepatic blood flow, promoting drug metabolism.[72]

Kawaguchi and associates showed that cyclosporine increased thromboxane A_2 urinary degradation products in rats bearing heterotopic cardiac allografts,[73] findings confirmed by Perico and co-workers.[74] Perico and co-workers also found that a thromboxane A_2 synthetase inhibitor (U-63557) improves but does not normalize renal blood flow. By administering 5-eicosapentaenoic acid as a codfish oil dietary supplement, Elzinga and colleagues deviated prostanoid metabolism to the generation of thromboxanes lacking vasoconstrictor properties, thereby mitigating nephrotoxicity in rats.[75] Foegh and associates prolonged allograft survival with the thromboxane synthetase inhibitor, OKY1581, or an active thromboxane receptor antagonist alone without cyclosporine.[76] Because increased thromboxane synthesis represents a common effector phase of rejection injury,[77] renal ischemia,[78] cyclosporine nephrotoxicity, and various renal diseases,[79] the exact mechanism of the observed prolongation is unclear. Concomitant pharmacologic therapy that alters cortical prostanoids seems to be a promising new approach. Because calcium may mediate the toxic effects of renal injury by influxing into anoxic arterial walls, mediating the vasoconstrictor effects of angiotensin II and promoting the generation of cytotoxic superoxides, calcium antagonists have been used to mitigate the adverse effect of cyclosporine on a freshly harvested, vulnerable kidney allograft. Iaina and co-workers reported that using verapamil reduced the severity of renal insufficiency and histologic damage caused by combined cyclosporine use and ischemia.[80] Administering the calcium antagonist diltiazem to cyclosporine-treated recipients immediately before transplantation and for two days afterwards reduced the incidence of delayed grafted function.[81] In addition, one-third lower doses of cyclosporine were needed because diltiazem interacts with cytochrome P-450,[82] interfering with cyclosporine metabolism. Further investigation of pharmacologic agents to improve the therapeutic index of cyclosporine will doubtless prove preferable to empiric trials of combinations of known immunosuppressive agents. Such studies must assess the effects of these regimens on both the immunosuppressive and the nephrotoxic potency of cyclosporine to assure that a reduction in toxicity is not accompanied by a reduction in therapeutic activity.

Clinical Cardiac Transplantation

HILLEL LAKS, MD,* and DAVIS C. DRINKWATER, MD†: The growth of cardiac transplantation is currently limited by the supply of donor hearts, which is adequate for less than 10% of the estimated 15,000 people a year who could benefit from the procedure.[11] The recent National Organ Transplantation Act has increased support of the regional organ procurement agencies and established a national registry to match donors and recipients,[83] but the imbalance will continue to worsen as the number of cardiac transplantation programs increases.

Criteria for acceptable donor hearts vary somewhat according to the priority status of recipients but are relatively

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standard (Table 4). The use of echocardiography to evaluate regional and global ventricular function may permit the use of some hearts that would otherwise have been rejected because of a history of chest trauma.[84]

More than half of the potential donor hearts are unacceptable due to apparent ventricular dysfunction.[85] In otherwise eligible donors, underlying cardiac disease is rare and the dysfunction seems to result from the acute systemic effects of central nervous system injury. Limitations of fluid volume and a reliance on inotropic support are necessary to maximize possible recovery after a cerebral injury but, unfortunately, may further compromise donor organs after brain death has occurred. A better understanding of the cardiac effects of head injury, such as reported in baboons, may permit improved cardiac preservation within a donor.[86] Most hearts are currently procured at a site distant from the recipient hospital. The currently accepted maximal ischemic time after the donor heart is removed is four hours. The duration of ischemia seems to correlate negatively with long-term survival.[85]

After the operation, many patients need low-dose catecholamine infusions to maintain their heart rate. The initial rhythm of the donor heart is frequently junctional or low atrial, with the gradual appearance of coordinated P waves. Pacing support is occasionally needed on a temporary basis, and on one occasion a permanent pacemaker was implanted in a patient who did not recover recognizable sinus node activity until six months postoperatively. Early postoperative electrocardiographic abnormalities are common, most likely reflecting acute denervation, but are rarely of clinical significance.[87]

Most patients are extubated within 24 hours and ambulatory at 48 hours. The postoperative course generally reflects the perioperative one. During the pretransplant period, most patients in our program are carefully maintained at a minimal fluid balance to minimize extravascular pulmonary, abdominal, and peripheral fluid. Of our 80 patients, major perioperative infection has developed in only 6. Mediastinitis has been a problem in some series but has thus far occurred only once in our population. The average postoperative hospital stay for our patients is 16 days during the entire program and has been 9 days for the last 20 adult patients. The 30-day survival is 96%.[9]

For a diagnosis of rejection, we depend on endomyocardial biopsy, using criteria modified from Billingham.[88] The increase in endocardial fibrosis and the number of previous biopsy sites causes progressive difficulty in acquiring adequate specimens. We are relying increasingly on computer-assisted measurement of two-dimensional echocardiograms, from which we have found an increase in the end-systolic volume or a decrease in the ejection fraction from individual patients' baselines to identify more than 75% of episodes of histologically documented moderate rejection.[89] Although some previous studies have reported that rejection affects diastolic more than systolic function,[90] we have found such echocardiographic measurements of relaxation less reliable than a serial quantification of systolic function. Rejection has been shown to decrease the ejection fraction also in serial radionuclide studies.[91] One of the advantages of doing routine systolic measurements is that patients are occasionally identified who have equivocal or normal biopsy results but nonetheless have depressed systolic function that improves after therapy for rejection. Immunologic monitoring for circulating activated lymphocytes has been a helpful adjunct to the monitoring of rejection in some centers.[92] Preliminary data suggest that antimyosin antibodies may be able to directly identify and quantitate cases of rejection noninvasively.[93]

TABLE 4.—*Standard Donor Criteria for Cardiac Transplants*

- Documented brain death in the absence of conditions of hypothermia or drug overdose
- Age younger than 35 for men, 45 for women*
- No evidence of chest trauma
- No history of cardiac disease, significant hypertension, or sustained cardiac arrest
- Inotropic requirement < 10 μg/kg/min with central venous pressure 5 to 10 cm H_2O
- No evidence of malignancy or infection
- Low risk for acquired immunodeficiency syndrome and, whenever obtainable, a negative screen for associated viruses
- Appropriate informed consent from family members
- ABO compatibility
- Comparable body size, within 20% height and weight, particularly when donor smaller than recipient
- Anticipated ischemic time < 4 h*

*These criteria are no longer absolute, particularly when transplantation is urgent.

Among our first 80 patients, there have been 110 episodes of rejection, with 10 patients being rejection-free. The expected average incidence is one episode per patient in the first three months and one episode in the following nine months. Programs in isolated areas of relatively homogenous ethnic populations may have a lower incidence of rejection due to better tissue compatibility. In our population, 106/110 episodes were treated successfully, which reflects the benefit of early diagnosis before significant injury and hemodynamic compromise. Of seven patients in whom cardiogenic shock developed due to rejection, three were successfully treated, the case of one having been previously reported.[94] Four of the patients admitted to recently discontinuing their immunosuppressive therapy. In patients receiving cyclosporine, rejection of this severity and rejection occurring after the first year are generally due to noncompliance.

The expected major infection rate is 1.5 episodes per patient for the first year, with a declining frequency thereafter. Superficial infections with *Candida* and herpesviruses are common but respond well to oral therapy. We have emphasized meticulous preoperative care and a minimal use of immunosuppressive drugs and have had only 33 significant infections, 80% of which have been successfully treated.

More than 85% of our long-term survivors are New York Heart Association class I. Transplanted hearts are able to respond adequately to circulatory demands despite the absence of direct autonomic innervation. The basal heart rate is usually 90 to 105 beats per minute because of the lack of vagal tone. Cardiac output increases immediately on initiating exercise because of the increased venous return.[95] The heart rate and the contractile state do not peak until at least five minutes, however, when circulating catecholamines have increased. The maximal oxygen consumption is lower than age- and size-predicted values and, in fact, is similar to that of patients with chronic heart failure who can be maintained on a stable afterload-reducing regimen.[96] Many cardiac transplant patients nonetheless engage regularly in demanding activities such as skiing, scuba diving, and even in one case the Boston marathon (a patient from the Harefield program, England).

Our one-year actuarial survival is 85%, with a two-year survival of 82%, which compares favorably with the overall survival in the International Heart Transplant Registry for patients treated with cyclosporine.[9] The main causes of death are infection and rejection. The general decrease in the severity of these during the first 90 days on cyclosporine therapy is the main reason for the overall increase in one-year survival from the 66% rate previously reported for patients on a regimen of azathioprine and prednisone.[9]

Relatively less progress has been made toward reducing the incidence of complications after the first year. Acute rejection is not a major cause of late mortality, except in cases of noncompliance, as discussed. The major problem remains accelerated graft atherosclerosis, as shown nine months after transplanting a 33-year-old donor heart into a 39-year-old man with idiopathic cardiomyopathy (Figure 2). Although a previous history of atherosclerosis and abnormal blood lipid values seems to increase the risk,[97] the major factor may be the nature of immunologic injury to endothelial surfaces. There is currently no evidence that the risk can be modified, but at UCLA patients are maintained on a regimen of aspirin, dipyridamole (Persantine), and a low-lipid diet, supplemented with low doses of lovastatin (mevinolin) in some cases, while hypertension and glucose intolerance, resulting in part from immunosuppressive medication, are aggressively treated.

Because of the diffuse distribution of atherosclerosis, its occurrence may be underestimated from coronary arteriograms but is currently estimated to be significant in 30% of patients after three years.[95] Thallium exercise studies may be of some help in screening patients with graft atherosclerosis, in whom angina does not occur. Although doing coronary artery bypass grafting is not appropriate due to poor distal vessels, angioplasty can occasionally be done to relieve ischemia when a specific focal lesion is present.[98] The rapidly progressive nature of atherosclerosis in patients afflicted frequently leads to sudden death or in some cases retransplantation.

Figure 2.—A left coronary angiogram is shown in the left lateral projection of a 33-year-old donor heart transplanted 10 months previously into a 39-year-old man with idiopathic cardiomyopathy. A 90% stenosis is seen in the left anterior descending artery **(curved arrow)** with sequential 90% stenosis in the circumflex artery **(large arrows)** and two adjacent 90% stenoses in the obtuse marginal branch **(small arrows)**.

Other late complications include malignancy, the prevalence of which is increased in all populations on immunosuppressive therapy. The reported incidence of malignancy in cardiac transplant recipients is 10%, of which skin cancer is the most common and lymphomas the second.[41] Most of the lymphomas are non-Hodgkin's lymphomas of B-cell origin, with extranodal sites, particularly brain and gastrointestinal tract, more common than in nontransplant patients with lymphoma. Lymphomas and Kaposi's sarcoma occurring in transplant patients may respond dramatically to a reduction of immunosuppression and are otherwise treated with standard chemotherapeutic regimens.

The overall five-year survival with cyclosporine therapy is currently 77%.[9] Evans and co-workers have estimated that the cost to Medicare per year of life gained from cardiac transplantation is $23,478, compared with $25,000 per year for renal dialysis and $110,000 per year for total parenteral nutrition.[11] Physical and psychologic function are eventually good for most patients, although the initial recovery from long periods of inactivity and dependency, which preceded the transplant, often stresses families. Although some patients return to work, many who are physically eligible do not obtain appropriate employment because of a financial dependency on the disability status and employers' concern about liability.[10] As the efficiency of cardiac transplantation becomes more widely appreciated by employers and their insurers, most transplant recipients should be able to enjoy professional as well as physical rehabilitation.

The major current limitation to cardiac transplantation is the scarcity of hearts, approximately one of which is available for every ten potential recipients.[11] With an increasing number of patients being referred for transplantation, it is vital that candidate selection and priority status be determined uniformly at all institutions.[18] Concern for the equitable distribution of limited donor hearts to those patients with the greatest expected benefit should eclipse institutional and regional affiliations. In addition, all transplant programs should be committed to design and maintain the optimal medical regimen for every patient referred to transplantation in order to minimize the number of urgent transplants and to maximize the status both of the patients awaiting transplant and of the greater number of patients who cannot receive them.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Geriatric Ambulatory and Institutional Care

James D. Lomax, MD, Director, Department of Family Practice, Long Island College Hospital, Brooklyn, New York. Ishiyaku EuroAmerica, Inc, 11559 Rock Island Ct, Maryland Heights, MO 63043, 1987. 209 pages, $27.50 (paperback).

This multiauthored paperback is intended to supplement traditional textbooks of geriatric medicine and gerontology. It is clearly not intended to be comprehensive or encyclopedic but rather, to cover ten topics that the authors thought were absent or inadequately covered in more traditionally formatted texts. As is common in multiauthored books, the utility of each chapter varies with the depth of coverage and quality of the writing. Most chapters have references; some are as recent as 1985.

After an introductory chapter on the demographics of aging, a chapter on health resources discusses Medicare, nursing homes, home care, hospices, day hospitals, and life care communities. These topics are briefly touched upon in a depth suitable for only the briefest of survey courses in gerontology.

The chapter on rehabilitation provides a good introduction to some elements of physical medicine, including the rudiments of prescribing assistive devices such as canes and wheelchairs. The advice shows common sense, and the illustrations in this chapter are useful. The chapter on geriatric dentistry gives an excellent introduction to a topic often stinted in medical education. A useful feature of this chapter is a section on medical-dental interactions, including aspects of dental care for patients on anticoagulant medication, with pacemakers, or undergoing radiation therapy and chemotherapy.

The chapter on urinary incontinence is brief but covers many important aspects of this major problem. The book includes an excellent and comprehensive chapter on sex and aging. The chapter on ostomy therapy is useful, covering material often lacking in standard geriatrics texts. The application of a problem-oriented systematic approach to the nursing care of elderly patients is also addressed in sufficient detail. A lengthy chapter on prescribing a physical activity program for older persons is comprehensive and may serve as a useful reference. One chapter stresses aspects of health care education pertinent to the elderly, and a brief chapter on death and dying offers some helpful advice concerning care of the terminally ill.

Overall, this book might serve as a useful adjunct to more comprehensive texts in an elementary course on geriatric medicine. The material is not covered in sufficient depth to satisfy the needs of geriatric fellows or other advanced students of this field. As the content of programs on geriatric medicine becomes better defined, the need for such a supplementary collection of topics will diminish as pertinent areas are added to more traditionally formatted textbooks.

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Editorial Comment

Cardiac Transplantation—The Need for Prospective, Randomized, Controlled Investigations

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In this issue of The Western Journal of Medicine, the aspects of cardiac transplantation that are critical to successful outcomes are discussed succinctly and in depth. Recipient and donor selection, allograft rejection immunoprophylaxis, the treatment of allograft rejection, and the management of infectious and late complications, such as allograft coronary artery disease, have been and remain the key issues of this complex treatment modality for end-stage heart disease. While expertise with the actual surgical procedure is an absolute requisite for success, it is nonetheless inadequate to guarantee short- and long-term survival. Because surgical mortality is less than 1% and the leading causes of death are infection, rejection, and allograft coronary artery disease,[1-4] future progress clearly depends on the refinement of the nonsurgical aspects of cardiac transplantation.

The evolution of cardiac transplantation to its present status as an accepted treatment option in selected patients with end-stage heart disease[5,6] depended on medical and surgical progress from the late 1960s to the present. During that time, most reported studies were from a single institution, were retrospective, and were uncontrolled or historically controlled. Despite these drawbacks, these investigations furthered the science and art of transplantation to the point that survival became routine.[1,2] The lack of randomized, prospective, controlled study methods and other factors, however, have led to a lack of uniformity in immunosuppressive protocols and have generated additional controversies in cardiac transplantation. In this communication, we discuss the complexities, controversies, and issues involved in recipient selection, immunosuppression, and governmental involvement in cardiac transplantation.

Recipient Selection

Due to the disparity between the number of potential recipients and the number of available donor hearts, recipient selection per se raises important societal and ethical concerns.[7] If donor hearts were plentiful, all patients who could benefit from the procedure would be considered for cardiac transplantation. Because a donor organ shortage exists, however, deciding in whom a donor heart should be used involves much more than a simple medical decision; it is a societal responsibility, one that the medical profession must actively participate in discharging. While the medical profession can show feasibility, it cannot unilaterally determine propriety. Should 70-year-old persons be denied transplantation on the basis of age alone because a younger person thereby loses the opportunity for benefit? Should persons with insulin-requiring diabetes be excluded from transplant consideration on the basis of quality-of-life issues even though the procedure would enable longer survival? Answers to these questions involve weighty issues that ethicists, moralists, and others will endlessly debate, and they do indeed require thoughtful consideration by all engaged in cardiac transplantation. Unfortunately, transplant physicians and surgeons cannot stand by, awaiting final, official resolution of donor-recipient ethical issues. Transplant physicians and surgeons must attempt to ensure that recipient selection is neither arbitrary nor inappropriately discriminating and that, in general, accepted candidates will be those in whom the use of scarce donor hearts leads to meaningful life.

Recipient exclusionary criteria have been relaxed in recent years due primarily to improved survival after cardiac transplantation. Criteria that once were absolutely contraindicatory have become only relative contraindications or no longer preclude transplantation.[5,8] The best example of criterion evolution is recipient age. In the early transplant experience, older persons had a higher incidence of morbidity and mortality, and most programs therefore excluded patients older than 45 years.[9-11] As results generally improved, however, older patients began undergoing cardiac transplantation. Recently it has been shown that older patients (up to age 65 years) have survival rates equal to or greater than their younger counterparts.[12,13] Thus, the medical profession has shown the feasibility of transplantation in patients as old as 65 years, and excluding patients from cardiac transplantation simply on the basis of age is not currently supported by the medical literature.

Immunosuppression

Clinical trials of immunosuppressive agents for use in organ transplantation are readily conducted in cardiac transplant recipients because the cardiac allograft lends itself to easier, safer, and more frequent biopsy than renal, hepatic, and pancreatic allografts. Unfortunately, however, prospectively randomized trials in cardiac transplantation are rare, leading each individual center to use different immunosuppressive protocols. The disparity among centers in immunosuppressive protocols is likely to remain until reproducible, appropriately conducted trials are reported.

(Renlund DG, Bristow MR, O'Connell JB: Cardiac transplantation—The need for prospective, randomized, controlled investigations. West J Med 1988 Nov; 149:583-585)

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ABBREVIATIONS USED IN TEXT

HCFA = Health Care Financing Administration
OPTN = Organ Procurement and Transplantation Network
UNOS = United Network for Organ Sharing

Because the cardiac allograft is amenable to biopsy, it should be possible to individualize recipient immunosuppression to strike the optimal balance in a particular patient with respect to allograft rejection and the risk of infection. The goal of immunoprophylaxis is to administer the lowest amount of immunosuppression that prevents allograft rejection, because any additional immunosuppression exposes the recipient to a higher risk of infection without any benefit.

Immunosuppression for cardiac transplantation can be divided into early prophylaxis, long-term maintenance, and the treatment of established allograft rejection.[14] Early prophylaxis refers to the immunosuppressive therapy given before cardiac transplantation and during the first two to three postoperative weeks. While many programs use T-cell cytolytic therapy (antithymocyte globulin, antilymphoblast globulin, or OKT3 monoclonal antibody), how aggressive early prophylaxis should be is currently debated. The three main purposes of early prophylaxis are the following[14]:

- To prevent or delay rejection during the period of time that the allograft is recovering from the ischemic insult that occurs during donor cardiectomy and recipient implantation because additional graft dysfunction due to rejection at this time might be fatal,
- To minimize the risk that rejection will occur while the recipient is recovering from surgical wounds, and
- To enhance the likelihood of the development of graft tolerance (engraftment) by the host's immune system, thus enabling the patient to be less immunosuppressed.

OKT3 monoclonal antibody may be the best T-cell-active agent in accomplishing all three main purposes of early prophylaxis.[15,16] When compared with antithymocyte globulin in a prospective trial, OKT3 monoclonal antibody not only significantly delayed the first episode of rejection but also decreased the overall number of rejections. Furthermore, early prophylaxis with OKT3 monoclonal antibody enabled the use of significantly lower doses of maintenance corticosteroids long term, to the extent that more than 80% of recipients are maintained without corticosteroids altogether, suggesting that early prophylaxis with this drug enhances graft tolerance.[15,17,18]

OKT3 monoclonal antibody is specific for the heterotrimeric CD3 surface antigen of peripheral T lymphocytes and presumably blocks antigen recognition. Because one mechanism of host recognition of donor antigen may occur by the presentation of donor "passenger" leukocytes to the recipient's reticuloendothelial system, blockade of antigen recognition sites by OKT3 monoclonal antibody until "passenger" leukocytes are cleared from the circulation may reduce the antigen load presented to the recipient.[18]

While long-term maintenance protocols also vary widely, Stevenson and co-workers describe an evolution from prednisone and azathioprine to cyclosporine and prednisone to triple therapy with cyclosporine, azathioprine, and prednisone.[19] Corticosteroid maintenance prophylaxis, however, is associated with many undesirable side effects, and a minimal use of corticosteroids may be desirable. Yacoub and associates were the first to begin using corticosteroid-free maintenance immunosuppression,[20] and it has recently been reported that more than 50% of patients may be successfully weaned completely off corticosteroid maintenance.[17] Patients successfully tapered off corticosteroid maintenance are leaner, less apt to be cushingoid, and less hypercholesterolemic, and they have only half the incidence of infectious complications when compared with recipients who are maintained on corticosteroid therapy.[17,19,21]

Governmental Involvement in Cardiac Transplantation

The federal government has in two ways recently become more involved in cardiac transplantation. First, it has decided to fund cardiac transplantation through the Health Care Financing Administration's (HCFA) Medicare program.[5] The funding of cardiac transplantation for Medicare recipients, while welcomed, has raised important questions regarding what constitutes acceptable results following cardiac transplantation.[6] As expected, no uniform agreement has been reached in the medical community. In response to HCFA's proposed one-year minimal survival rate of 73% for a transplant program to be eligible for Medicare funding, many in the medical community argued for a higher minimum standard, while others argued that a high standard would inhibit clinical progress and make it more difficult for a high-risk patient to receive a needed transplant.[5] It should be noted that patients with severe hemodynamic compromise at the time of transplantation do not appear to have a significantly different survival rate from that of their less hemodynamically compromised counterparts.[6,22,23] Furthermore, it seems unlikely that significant clinical progress will emanate from centers that are unable to achieve one-year actuarial survival rates substantially higher than 73%. While the use of donor hearts in situations in which the chance of meaningful survival is low might be intellectually, academically, or humanistically appealing, this desire must be balanced with the realization that doing so denies the opportunity for benefit to potential recipients in whom the likelihood of success is higher.

Even though HCFA has attempted to define numerically what constitutes a successful program, the overall success of cardiac transplantation as a treatment for end-stage heart disease is best assessed using the intention to treat analysis-of-survival curves. All aspects of cardiac transplantation, including donor heart procurement and allocation, would affect this easily measured variable. A transplant program with a survival following transplantation of 90% but a 70% mortality for recipients awaiting cardiac transplantation has an approximately 27% survival by intention to treat and is less successful than a program that has a 10% mortality in recipients awaiting transplantation and an 80% survival following transplantation, resulting in an approximately 72% survival by intention to treat.

A second aspect of federal involvement in cardiac transplantation emerged when the Congress of the United States established a national Organ Procurement and Transplantation Network (OPTN), under the Public Health Service Act, with the expressed purpose of improving the effectiveness of the nation's renal and extrarenal organ procurement, distribution, and transplantation systems. The OPTN contract was awarded to the United Network for Organ Sharing (UNOS), a private, nonprofit Virginia corporation that has been given the responsibility of accomplishing what professional organizations, individual states, and the nation have been unable

to accomplish since the beginning of clinical organ transplantation: to effect the equitable distribution and effective use of scarce donor organs. Impediments and stumbling blocks to the success of UNOS in accomplishing its charges have come from professional organizations, individual transplant centers, governmental administrative agencies, and congressional delegations and at some point will undoubtedly involve the judicial systems of our nation.

To receive information and advice from the heart transplant community, UNOS, which formerly comprised mostly persons involved in renal transplantation, formed the Heart Transplantation Advisory Committee as a permanent standing committee and assigned individuals from the heart transplantation committee to their Organ Procurement and Distribution Committee and their Membership and Professional Standards Committee. Thus, this private corporation assigned the task of the equitable and effective use of donor hearts has been responsive to the heart transplant community. Whether UNOS will be successful in discharging its responsibility remains to be determined. If UNOS fails, the alternative will be that organ allocation will be regulated by a federal agency that would likely be less responsive to the heart transplant community than UNOS has been.

Conclusion

While many ethical dilemmas remain, cardiac transplantation prolongs life and improves the quality of life. Now that the Stanford University Medical Center and a few other centers have worked out the basics of cardiac transplantation that have resulted in routine survival, it is time to conduct more careful, controlled studies to resolve controversies and advance the art and science of cardiac transplantation further.

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Fulminant Hepatic Failure

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Fulminant hepatic failure is a dramatic, severe disorder that is frequently, but not uniformly, fatal. Remarkably, survivors usually recover normal hepatic function. New hope for those with progressive, severe disease is offered by liver transplantation, a procedure recently reviewed in a Medical Staff Conference by Nancy Ascher, MD.† This conference's review of fulminant hepatic failure will be given by Randy Yanda, MD, who has served with grace and distinction as a chief medical resident over the past year.*

RANDY J. YANDA, MD‡: Fulminant hepatic failure is the clinical syndrome associated with massive necrosis of liver cells or sudden, severe impairment of hepatic function. There is no clear inclusive definition of the disorder. The most commonly used definition is "hepatocellular dysfunction of such severity that encephalopathy occurs within eight weeks of appearance of first symptoms in the absence of preexisting liver disease."[1] This definition has three major parts: there must be enough liver dysfunction that encephalopathy occurs, encephalopathy must occur within eight weeks, and there must be no history of preexisting liver disease. The time course in this definition is arbitrary and excludes patients with a more protracted course who would receive the diagnosis of subfulminant or late-onset hepatic failure. It is becoming increasingly clear that there is a spectrum of patients regarding the time encephalopathy occurs, from those having an early start of encephalopathy (often with hepatitis A) with a good prognosis to those in whom encephalopathy develops at eight weeks or later (usually with non-A, non-B hepatitis) with a poor prognosis.[2] The absence of preexisting liver disease implies, and it is generally the rule, that liver structure and function will return to normal if the patient survives.

Fulminant hepatic failure is an uncommon disease; the number of cases in the United States has been estimated to be fewer than 2,000 per year.[3] The incidence of the disorder in patients admitted to the University of California, San Francisco (UCSF), however, has risen since UCSF has become a liver transplantation center. The approach to the management of these patients has changed as liver transplantation becomes an accepted treatment of this disease.

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†"Liver Transplantation—The First 25 Years (Medical Staff Conference)," *West J Med* 1988 Sep; 149:316-321.

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Etiology

Fulminant hepatic failure is caused by viral hepatitis, drug reactions, or poisonings in more than 90% of cases. Table 1 lists all but the rarest causes of the disease. In Western countries about 80% of cases are due to hepatitis virus infections; of these, hepatitis B virus is the most common.[4] The frequencies of the major causes of fulminant hepatic failure are listed in Table 2.

Fulminant hepatitis A is uncommon but does occur. The risk of its developing in the course of symptomatic acute hepatitis A is 0.01% to 0.1%[5] Among patients in the US with the disorder, the incidence of hepatitis A is 2% to 4%.[6] It usually develops early in the course of hepatitis A and tends to occur in older patients. It is associated with a relatively good survival rate of more than 40%.[7] Hepatitis B, either alone or together with hepatitis D (delta agent), is the major cause of fulminant hepatic failure in this country.[6] Most cases occur in young adult drug addicts and their sexual partners. It rarely develops in homosexual or bisexual men, in whom infection with hepatitis B is common.[5]

It is unclear why in some patients acute viral hepatitis B progresses to fulminant hepatic failure. There appears to be a rapid clearance of all three hepatitis antigens with a rapid, enhanced production of antibodies to the hepatitis B surface antigen (HBsAg), the e antigen, and the core antigen.[8] Hepatitis B virus DNA measured in serum, which is thought to be a sensitive measure of active viral replication, is less frequently found in patients with fulminant hepatic failure than in those with nonfulminant disease.[9] These studies suggest that viral replication is interrupted early in patients with fulminant disease and that an immunologic mechanism may be responsible for the massive destruction of liver parenchyma. It has been postulated that because the spleen is the major site of antibody production, the portal circulation of antibodies is high and their combination with viral antigen released from damaged hepatocytes can cause an Arthus reaction in the hepatic sinusoids leading to ischemic necrosis.

Hepatitis D virus is a defective hepatotropic RNA virus that requires the presence of the hepatitis B virus to be pathogenic. Therefore, if persons are immune to the hepatitis B virus, they are immune to the hepatitis D virus as well. In Western countries with low hepatitis B endemicity, hepatitis D infection is virtually confined to parenteral drug addicts and to high-risk populations of HBsAg carriers (persons with hemophilia, hemodialysis patients, and the like).[10] Acute infection with hepatitis D can develop either as a coinfection

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ABBREVIATIONS USED IN TEXT

HBsAg = hepatitis B surface antigen
UCSF = University of California, San Francisco

with hepatitis B or as a superinfection in patients with an underlying chronic hepatitis B infection.[11] Most cases of fulminant hepatic failure due to infection with hepatitis B and D appear to be simultaneous infections.[12] About a third of patients with fulminant hepatitis B have coexisting hepatitis D infection as compared with 4% of patients with nonfulminant hepatitis B.[12] Therefore, it appears that the risk of fulminant hepatic failure developing due to infection with hepatitis B is increased if hepatitis D is present, but the mortality of the disorder is similar whether due to hepatitis B and D or hepatitis B alone.

Non-A, non-B hepatitis is a diagnosis of exclusion. The diagnosis is made in the absence of serologic evidence of a recent infection with hepatitis A, B, or herpesvirus, or of a recent ingestion or exposure to drugs or chemicals known to be toxic to the liver. Its contribution to fulminant hepatic failure cannot be assessed accurately in the absence of serologic tests. The percentage of patients with fulminant hepatic failure thought to be caused by non-A, non-B hepatitis is about 24% to 34%.[5] These patients tend to have a longer period between the onset of symptoms and encephalopathy and have a poor prognosis.[7] In general, severe, acute, and fulminant non-A, non-B hepatitis is rarely encountered. Patients with fulminant hepatic failure thought to be caused by non-A, non-B hepatitis rarely have risk factors for this infection (history of blood product transfusion). This is supported by the observation that no deaths associated with acute non-A, non-B hepatitis occurred in 515 patients with post-transfusion hepatitis.[13] The actual contribution of non-A, non-B hepatitis as a cause of fulminant hepatic failure will become clearer as serologic tests become available to detect the agent(s) that cause the disease.

Ingesting amatoxin-containing mushrooms is a common cause of poisoning resulting in hepatic damage in the San Francisco Bay Area (22 reported cases from 1982 and 1983).[14] The most common amatoxin-containing mushroom in northern California is *Amanita phalloides.* It has been found in increasingly larger quantities over greater areas of California and grows best when warm weather follows heavy rains. Typically in cases of mushroom poisoning, severe abdominal cramping, vomiting, and profuse diarrhea begin 6 to 24 hours after ingestion. This is followed by a latent phase over the next 24 to 36 hours when there is a remission in symptoms and the patient appears to be recovering. The patient then exhibits clinical hepatitis with jaundice that may subsequently progress to fulminant hepatic failure.

The popularity of acetaminophen as a suicidal agent in England makes it a common cause of fulminant hepatic failure in that country. Obstruction of the large hepatic veins (Budd-Chiari syndrome) or the centrilobular veins (veno-occlusive disease) may present as fulminant hepatic failure and is uniformly fatal. Hepatic failure can also be the first clinical manifestation of Wilson's disease. This is mainly seen in patients younger than 20 years who have no previous evidence of neurologic manifestations and is classically associated with intravascular hemolysis. Fulminant liver failure in Wilson's disease had been uniformly fatal, but liver transplantation appears to be an effective treatment of this disorder, as will be discussed.

TABLE 1.—*Principal Causes of Fulminant Hepatic Failure*

Infections	Vascular Causes
Viral hepatitis	Ischemic liver cell necrosis
Type A	Pericardial tamponade
Type B	Obstruction of the hepatic veins
Non-A, non-B	Budd-Chiari syndrome
Type D (delta agent)	Veno-occlusive disease
Coinfection	Heatstroke
Superinfection	Miscellaneous
Drugs, Chemicals, Toxins	Microvesicular steatosis
Amatoxin-containing mushrooms	Reye's syndrome
Industrial solvents	Acute fatty liver of pregnancy
Acetaminophen	Wilson's disease
Tetracycline	Malignant infiltration of the liver
Halothane	
Isoniazid	
Methyldopa	
Sodium valproate	

Mortality and Prognosis

Fulminant hepatic failure is a severe but not uniformly fatal syndrome. It is difficult to arrive at a satisfactory survival rate because many of the reported figures include patients who have received experimental therapy. If the rates for patients receiving placebo in several prospective controlled trials are combined with those in studies of supportive therapeutic regimens to eliminate treatment bias, a survival rate of 27% is obtained (Table 3).[15-20] These studies did not consider liver transplantation, however, which appears to significantly alter mortality. The survival rate in patients with fulminant failure due to hepatitis A, hepatitis B, and acetaminophen poisoning has improved over time at one major liver unit.[20] This has been attributed to better management of the frequent complications seen in patients with the disorder and better intensive unit care. On the other hand, patients with failure due to non-A, non-B hepatitis, the use of halothane, and other drug reactions have not had a similar improvement in survival at the same unit over the same time period. Differentiating patients who will have poor survival

TABLE 2.—*Frequency of Major Causes of Fulminant Hepatic Failure*

Cause	Cases, %	Cause	Cases, %
Hepatitis A	2-4	Drugs	6-15
Hepatitis B	60-75	Poisonings	1-2
Non-A, non-B hepatitis	24-34	Miscellaneous	0-10

TABLE 3.—*Survival Rates of Patients With Fulminant Hepatic Failure*

Study	Patients, No.	Patients Survived, No. (%)
Redeker et al, 1976[15]	16	6 (38)
Acute Hepatic Failure Study Group, 1977[16]	28	9 (32)
European Association for the Study of the Liver, 1979[17]	14	2 (14)
Rakela et al, 1985[18]	34	2 (6)
Tandon et al, 1986[19]	145	42 (29)
O'Grady et al, 1988[20]	33	13 (39)
Total	270	74 (27)

rates is important because they may be good candidates for early liver transplantation. It can be expected that about a third of patients will die within two days of the beginning of stage IV coma.[1]

Considerable effort has been made to identify factors that may be used to estimate the chances of survival in an individual patient. This has become even more important as liver transplantation has become an accepted therapy for this condition. The early detection of an extremely poor prognosis may allow for transplantation before multiple organ system failure occurs. Most of the relevant literature consists of retrospective analyses of single observations seen in survivors and nonsurvivors. Clinical variables that have been found to be significantly useful in predicting death include age, the stage of coma, and the cause of the fulminant liver failure.[21] Mortality in patients older than 45 years is roughly 95%. Survival in patients who present in stage IV coma is less than 10% but is significantly higher if the patient has stage I or II encephalopathy. Serum bilirubin and glucose values and a prothrombin time, which reflect liver function, are also useful. The development of complications such as renal failure, hypotension, and substantial hemorrhage is predictive of nearly 100% mortality.[21]

Normal hepatic function and structure are usually completely restored in survivors of fulminant hepatic failure, with biochemical liver test results and liver histologic appearance returning to normal within 45 to 75 days.[3] In rare cases, second attacks of acute viral hepatitis will occur four to ten months after an episode of fulminant hepatic failure, but these are generally milder than the initial infection. A few patients have been reported to have chronic active hepatitis after surviving fulminant liver failure, but this is also considered rare.[22]

Complications

In patients with this disorder, a large number of complications will develop involving several organ systems. The appropriate management requires an intensive care unit, preferably at a center experienced in the treatment of liver failure. To reduce the mortality to a minimum, physicians should have an understanding of the pathophysiology and treatment of these complications.

Hepatic encephalopathy is a universal complication in fulminant liver failure, as it is required for the diagnosis. A discussion of the pathophysiology and treatment of this disorder is beyond the scope of this paper, and readers are referred to several recent reviews of this subject.[23,24] A guide for the clinical stages of hepatic encephalopathy is shown in Table 4. Patients with stage I encephalopathy are generally alert and have mainly neuropsychiatric disturbances. Speech may be affected and disturbances of sleep rhythm may be a prominent symptom. Patients with stage II encephalopathy are drowsy but will respond appropriately to simple commands if given enough time. They show little interest in their surroundings and may appear apathetic about events around them. They also may have amnesia for recent events, and it is in this stage that asterixis often appears. Patients with stage III encephalopathy sleep when left alone but are able to be aroused. They are usually extremely confused and speak incoherently. If patients recover, they have no recollection of events that occurred during this stage. Physical findings in patients with stage III encephalopathy include hyperactive deep tendon reflexes, an increased muscle tone, and pupils

TABLE 4.—*Clinical Stages of Hepatic Encephalopathy*

Stage	*Mental State*
I	Euphoria, occasional depression
	Fluctuant, mild confusion
	Slowed mentation and affect
	Untidy, slurred speech
	Disordered sleep rhythm
II	Drowsy but responds to simple commands
	Inappropriate behavior
III	Sleeps most of time, but arousable
	Marked confusion, incoherent speech
IV	Unarousable, may or may not respond to noxious stimuli

that are small and sluggishly reactive. Finally, patients in stage IV coma are unarousable and may or may not respond to noxious stimuli. Their muscle tone becomes flaccid, and their pupils become dilated but remain sluggishly reactive. None of these symptoms or signs are specific for hepatic failure as they all can be seen in other metabolic derangements that affect the central nervous system. An electroencephalogram in these patients is also nonspecific. There is slowing of the dominant frequency in proportion to the degree of encephalopathy. In stage IV coma, there may be no detectable electrical activity. Generally, cleansing the bowel with the use of lactulose is recommended in addition to correcting electrolyte abnormalities and avoiding giving neuroactive drugs. Neomycin should not be administered as it is potentially nephrotoxic.

Cerebral edema is a frequently occurring complication in this disorder and is a major cause of death. Cerebral edema diagnosed clinically or by a rise of the intracranial pressure of more than 30 mm of mercury by intracranial pressure monitoring occurred in 85% of patients in one study.[25] While it is a common complication in acute liver failure, cerebral edema is rarely seen in patients with encephalopathy from chronic liver disease. It is also important to note that the development of cerebral edema is almost entirely restricted to stage IV encephalopathy.

The diagnosis of an increased intracranial pressure is made by a careful neurologic examination with the help of intracranial pressure monitoring. An early neurologic sign of increased intracranial pressure is an increase in the muscle tone in the arms and legs. Most patients will show substantial hyperventilation, with pupils that are dilated and sluggishly reactive to light. As the intracranial pressure continues to rise, the increase in muscle tone will progress to full decerebrate posturing with hyperpronation and adduction of the arms. Failure to interrupt the process at this point is likely to result in respiratory arrest and brain-stem herniation. Changes in pupillary responses are a particularly reliable sign of increased intracranial pressure. This is especially the case in patients requiring mechanical ventilation in whom muscle rigidity and decerebrate posturing are masked by the effects of muscle-paralyzing drugs.

Continuous monitoring of the intracranial pressure by subdural or extradural pressure transducers should enable an early recognition of cerebral edema and therefore allow for treatment to be started at a possibly reversible stage. Extradural monitors are used at UCSF and at most other liver transplant centers and provide accurate measurements with a minimal risk of complications. Continuous monitoring is especially important during an actual liver transplantation

because of the wide swings of intracranial pressure that commonly occur during the operative procedure. Because most patients with fulminant hepatic failure who need intracranial pressure monitors have a severe coagulopathy, the prophylactic administration of fresh frozen plasma is indicated before placing these monitors.

There are several measures that can be taken to prevent cerebral edema in these patients. A patient's movements should be restricted because rapid changes in position can exacerbate an increased intracranial pressure and can precipitate brain-stem herniation. Careful management of the administration of intravenous fluids is essential to avoid a fluid overload that will increase the intracranial pressure. Blood gas values should be checked frequently to avoid hypoxia and hypercarbia. Because of the influence of posture on the intracranial pressure, the upper half of the body should be kept at an angle of 30 to 40 degrees above the horizontal. Special care should also be taken to avoid occluding venous return from the head—that is, extreme flexion, extension, or rotation of the head or occlusion of the jugular veins while securing the endotracheal tube with tape.

An increased intracranial pressure should be treated once it has reached a persistent level of 30 mm of mercury.[26] The treatment of cerebral edema in patients with fulminant hepatic failure differs from that in patients with other causes of elevated intracranial pressure—head trauma or brain tumor—because not all treatments are effective in this disorder. Hyperventilation is effective by decreasing the cerebral blood flow. Short-term mechanical hyperventilation is effective in lowering the intracranial pressure in these patients, but this effect will last for only 48 to 72 hours.[26] A prospective, randomized study failed to show any benefit of prophylactic mechanical hyperventilation in preventing cerebral edema in patients in stage III encephalopathy.[26] Therefore, these patients should not be mechanically hyperventilated until they have evidence of an elevated intracranial pressure by clinical examination or direct measurement by an intracranial pressure monitor.

The use of corticosteroids is not effective in preventing or treating cerebral edema in these patients,[26] but administering mannitol does lower the intracranial pressure. It should be infused rapidly at a dose of 0.5 to 1.0 gram per kg body weight to achieve its maximum effect. It must be used with caution in patients with renal insufficiency because fluid overload and hyperosmolarity can result that would further worsen the cerebral edema. If the urine output is low in response to a mannitol infusion, the plasma osmolarity must be checked and should not exceed 320 mosm per kg. Hemodialysis is indicated to remove volume in patients with renal failure who require mannitol therapy for an elevated intracranial pressure. Barbiturates will decrease the intracranial pressure by decreasing the cerebral blood flow but may be difficult to use because of their effects on the systemic blood pressure. The use of barbiturates will also further depress a patient's mental state and make it difficult to follow the course of liver failure.

Patients with fulminant liver failure almost universally have a severe and complex coagulopathy. The liver has a central role in coagulation because it is responsible for the synthesis of most of the clotting factors and also clears activated clotting factors from the bloodstream. All clotting factor concentrations are decreased in patients with this disorder, except that of factor VIII, which is increased.[27] Thrombocytopenia is common, and platelet studies show abnormalities in aggregation and adhesion. The role of disseminated intravascular coagulopathy in patients with this syndrome is controversial. In one study heparin therapy did not reduce the incidence of extensive bleeding.[27] Bleeding occurs in as many as 75% of patients and is severe in 30%. It is most common from the gastrointestinal tract, usually from gastric mucosal erosions. Other sites include the nasopharynx, lungs, retroperitoneum, kidneys, and skin puncture sites. Administering cimetidine in doses sufficient to maintain the gastric pH above 5.0 has been shown to reduce transfusion requirements in these patients.[28] Blood loss should be replaced with whole blood in view of its greater concentration of coagulation factors and platelets. The prophylactic administration of fresh frozen plasma in patients without bleeding has not been shown to reduce morbidity or mortality in patients with this disorder.[27] Surgical and invasive procedures are an indication for fresh frozen plasma and platelet transfusions before the procedure if the prothrombin time is substantially prolonged.

Acute renal dysfunction is a common and ominous complication occurring in as many as 50% to 75% of patients with fulminant hepatic failure. There is a spectrum of renal lesions from functional renal failure (hepatorenal) to acute tubular necrosis. Features of acute tubular necrosis in this syndrome include numerous granular and cellular casts in the urine, a urinary sodium concentration of more than 20 mmol per liter, and a urine:plasma urea concentration ratio of less than 10. Features of the functional renal failure in fulminant hepatic failure include normal urinary sediment and a urinary sodium concentration of less than 20 mmol per liter. The relative frequency of these lesions is about equal.[29] The serum creatinine concentration is a better index of renal function than the blood urea nitrogen value because urea synthesis is greatly decreased in these patients. Hemodialysis may be indicated in patients who are liver transplant candidates because functional renal failure may be reversible after liver transplantation.[30]

In fulminant hepatic failure there is a severe circulatory disturbance characterized by a low systemic vascular resistance with a compensatory increase in the cardiac output. This leads to overt hyperdynamic shock leading to further organ dysfunction. The pathogenesis of this complication is unknown. Relative hypovolemia is common and must be corrected, as well as any electrolyte disturbances. Administering pressors has not been shown to benefit patients with the disorder.[29] Arrhythmias also are common, occurring in more than 90% of patients in stage IV coma.[31] A postmortem examination of the heart reveals abnormalities in most patients, including scattered petechial hemorrhages, pericardial effusions, and fatty, pale, and flabby ventricles.

Pulmonary complications are also seen in these patients. Early in the course of the disease, most patients will hyperventilate with resultant hypocapnia. Later there appears to be a high incidence of low-pressure pulmonary edema (adult respiratory distress syndrome) involving about a third of patients.[29] This complication develops at an average of four days after the beginning of stage IV coma. The incidence of pulmonary edema tends to be higher in patients with cerebral edema, suggesting that there is a common factor causing both complications or that increased intracranial pressure may contribute to the formation of pulmonary edema. Mechanical ventilation with positive end-expiratory pressure is

usually required to support oxygenation but may be harmful by reducing hepatic blood flow, primarily by decreasing cardiac output. Hemodynamic monitoring is indicated in these patients to assure optimal therapy.

Metabolic abnormalities include severe hypoglycemia—a blood glucose value less than 2.2 mmol per liter (40 mg per dl)—which occurs in about 40% of patients in fulminant hepatic failure.[3] It is particularly common in children with this syndrome. The amount of intravenously administered dextrose needed to correct the hypoglycemia may be enormous—as much as 2 kg per day. Hypoglycemic coma can occur independent of hepatic coma and should be suspected whenever there is an abrupt deterioration of the mental state in these patients. A wide spectrum of acid-base disturbances occurs in association with the disorder. Spontaneous hyperventilation is common and may lead to a respiratory alkalosis. Extensive tissue damage, often with accompanying hypotension, produces an accumulation of lactic acid and other organic acids that may result in a metabolic acidosis. Hyponatremia is often present despite an increased renal retention of sodium. The inability of the kidneys to excrete appropriate amounts of free water also contributes to the development of hyponatremia. Hypokalemia often accompanies hyponatremia and is associated with an increased plasma concentration of bicarbonate producing a metabolic alkalosis.

Patients with this syndrome also have an increased prevalence of bacteremia.[32] When bacteremia occurs it is not necessarily accompanied by fever or other typical clinical or laboratory features of sepsis. Therefore, these patients need frequent invasive microbiologic monitoring with culturing of blood, sputum, and urine specimens. Altered host factors, including disorders of neutrophil function, mechanical invasion of host defenses, and corticosteroid therapy, contribute to this complication.

Treatment

There are several general treatment guidelines that should be emphasized and followed in all patients with fulminant hepatic failure. If possible, all patients should be transferred to a tertiary care facility, preferably one that is a liver transplant center. The transfer should be early in the course of the disease, ideally in stage I or II encephalopathy. This is important because it allows time for a liver transplant team to evaluate the patient and decide whether he or she is a transplant candidate. It also allows time to locate a donor liver. Appropriate blood specimens should be sent to the blood bank and laboratory for serologic testing. An acetaminophen concentration is mandatory in all patients when they present in fulminant hepatic failure. Although it is usually too late to treat for acetaminophen poisoning by the time a patient presents in liver failure, it is important to document the cause of the liver disease because the prognosis may be better in acetaminophen poisoning than in other causes, such as non-A, non-B hepatitis or Wilson's disease. Corticosteroids should not be used in these patients because they are not effective in treating the hepatitis or the cerebral edema and they may increase the susceptibility to infection. Sedative-hypnotic agents should also be avoided because they alter a patient's mental state and make it difficult to follow the course of liver failure. The prophylactic use of coagulation-factor concentrates has not been shown to be effective in preventing bleeding. Vitamin K should be given to attempt to correct the coagulopathy, and sufficient H_2-receptor blockers should be administered to maintain the gastric pH above 5.0. If an elevated intracranial pressure is diagnosed, mechanical hyperventilation should be started and mannitol should be given as needed to keep the intracranial pressure below 30 mm of mercury.

A substantial amount of work has been done to develop a workable "artificial liver." The goal of this device is to keep patients with fulminant hepatic failure alive until their liver has regenerated sufficiently or until a liver transplant can be done. In theory, a suitable detoxification system would remove toxic substances accumulated during the course of liver failure that are normally removed by the liver, including those tightly bound to albumin. An effective detoxification system has great appeal because removing toxins from the bloodstream would allow time for the liver to regenerate and possibly prevent some of the complications of the syndrome. The ability to maintain a patient on an artificial liver should enable more patients to be transplanted because time would be less of a factor. Charcoal hemoperfusion has probably been the system that has been studied most extensively, primarily by the group at King's College Hospital in London. They have reported increased survival in patients with acetaminophen-induced fulminant hepatic failure in stage III coma versus historical controls.[33] An improved mental state and a decreased frequency of cerebral edema have also been reported in other uncontrolled studies.[34] A recently published, randomized, prospective trial from the King's College Hospital group, however, showed no significant improvement in mortality with the use of charcoal hemoperfusion in patients with stage III or IV coma.[20] This study is especially important because it comes from the group that has enthusiastically advocated this therapeutic method over the past decade. Two other therapies, plasmapheresis and hemofiltration, have also been reported to improve mental state during the procedure,[35,36] but prospective studies have not been carried out to show a significant decrease in complications or mortality. From the literature published to date, it is reasonable to conclude that artificial liver support systems may be valuable in the future but, at present, should be considered experimental.

The role of liver transplantation as an accepted therapy for this disorder has emerged in the past few years, although the first liver transplantation for the syndrome was done in 1968.[37] The patient was a 17-year-old boy who had fulminant liver failure from viral hepatitis and was in stage IV encephalopathy. After the operation he regained consciousness, but immunosuppressive drugs were withheld because reactivation of the viral hepatitis was feared, and he died of acute rejection on the sixth postoperative day. Over the past 20 years, knowledge of the pathogenesis of the disorder and transplantation techniques have greatly improved. Six recent publications from liver transplant centers have reported a significant improvement in the survival of these patients who received transplants as compared with survival in historical controls (Table 5).[37-42] In planning the timing of transplantation, it must be taken into consideration that, although fulminant hepatic failure has a high mortality rate, a patient can recover fully without significant liver disease. Patients with the syndrome due to non-A, non-B hepatitis, hepatotoxic drug reactions (other than acetaminophen), fulminant Wilson's disease, and so-called late-onset hepatic failure seem to have a particularly poor prognosis and may be the best candi-

TABLE 5.—*Orthotopic Liver Transplantation in Patients With Fulminant Hepatic Failure*

Authors or Institutions and Year	*Patients Transplanted, No.*	*Patients Survived, No. (%)*
King's College Hospital, 1986[39]	16	10 (63)
Adams et al, 1986[38]	3	2 (67)
Pittsburgh, 1987[40]	13	7 (54)
Bismuth et al, 1987[41]	23	17 (74)
Brems et al, 1987[37]	6	4 (67)
Mayo Clinic, 1988[42]	8	5 (63)
Total	69	45 (65)

dates for early transplantation.[2,6,7,42] The consideration of when to transplant should be tailored to each case, as there are no reliable criteria that will identify a subset of patients who might recover. A persistently prolonged prothrombin time of more than 20 seconds for two weeks or more, hypoglycemia, gastrointestinal bleeding, progressive renal failure, and progressive encephalopathy despite maximal nutritional and blood product support are advanced complications and warrant urgent transplantation.[43]

When a patient with fulminant hepatic failure requires an orthotopic liver transplant, the most important aspect in matching donor to recipient is size. The operative procedure is actually less difficult in these patients than in those with chronic liver disease because there are fewer adhesions and venous collaterals and less ascites.[42] Most patients have a prompt resolution of coma and are extubated soon after transplantation without an apparent neurologic deficit. In cases due to viral hepatitis, the risk of recurrence may be substantial, but usually it is not of the fulminant variety. Complete recovery with a disappearance of HBsAg and the appearance of anti-HBsAg after transplantation has been reported in a young man with the syndrome due to acute hepatitis B.[44] In summary, liver transplantation appears to significantly improve mortality in patients with fulminant hepatic failure when compared with historical controls and has now become an accepted therapy for this condition.

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Epitomes

Important Advances in Clinical Medicine

Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Platelet Antibodies

THROMBOCYTOPENIA may occur as the sole manifestation of disease or may be due to another disorder. The management of either primary or secondary thrombocytopenia depends on correctly identifying the causal pathophysiologic processes. Over the past decade a number of research laboratories have provided data to strongly support the hypothesis that primary isolated thrombocytopenia in adults—idiopathic thrombocytopenia purpura—is immune-mediated and in many cases may be more correctly termed autoimmune thrombocytopenia purpura. The development of sensitive assays that directly measure platelet-associated immunoglobulin (PAIg) corroborated earlier studies which suggested that this disorder is due to the deposition of immunoglobulin on the platelet surface, leading to the accelerated clearance of sensitized platelets. The ability to directly measure PAIg, in contrast to the earlier tests for detecting serum antiplatelet factors, has increased the sensitivity from 60% to greater than 90% with 93% specificity for detecting immune-mediated platelet destruction.

The increased diagnostic sensitivity has raised new questions concerning the specificity of elevated PAIg levels. It is now well recognized that increased PAIg can occur in thrombocytopenia associated with a wide variety of disorders, including systemic lupus erythematosus, lymphoma, carcinoma, Hodgkin's disease, the acquired immunodeficiency syndrome, and Hashimoto's thyroiditis. Elevated PAIg levels also may be associated with qualitative platelet dysfunction without concurrent thrombocytopenia. Thus, elevated PAIg levels are not specifically associated with isolated autoimmune or idiopathic thrombocytopenia purpura. In most cases, it is unclear whether PAIg noted in either autoimmune thrombocytopenia purpura or the secondary disorders is specifically directed against a platelet antigen or is nonspecifically deposited on the platelet surface as part of an immune complex. In several recent reports the use of immunoblot techniques has identified PAIg directed against integral platelet proteins in some patients with autoimmune thrombocytopenia purpura. A recent study using monoclonal reagents for the detection of cell-associated immunoglobulin has provided stronger evidence that the presence of elevated levels of PAIg—more than 800 molecules of IgG per platelet—is physiologically consistent with currently understood immune-mediated clearance of other blood cells, and this concentration of cell-associated immunoglobulin is not observed in patients with nonimmune thrombocytopenia.

Each of the different techniques described to measure PAIg requires isolating platelets from whole blood, which may be difficult in patients with severe thrombocytopenia. Newly described fluorescence-activated flow cytometric assays and radioactive immunologic assays, however, exhibit adequate sensitivity even when few platelets are available. Indirect tests may be useful to diagnose neonatal isoimmune thrombocytopenia, post-transfusion purpura, or transfusion-induced alloimmunization. Indirect assays for determining suspected drug-dependent immune thrombocytopenia have had disappointing results due to the inability to solubilize drugs and do the assays under physiologic conditions. In summary, the direct measurement of platelet-associated immunoglobulin is useful in establishing the diagnosis of immune-mediated platelet destruction and in choosing among various therapeutic alternatives during the course of these disorders.

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Fine-Needle Aspiration Biopsy of Lymph Nodes

FINE-NEEDLE ASPIRATION (FNA) or aspiration biopsy cytology of lymph nodes is done in patients presenting with persistent lymphadenopathy for which no obvious explanation exists, to stage patients with previously diagnosed malignancy (including malignant lymphoma), and to monitor for recurrence and progression of disease. Within this setting, a diagnosis of infection, reactive hyperplasia, malignant lymphoma, and metastatic tumor is sought.

The diagnosis of metastatic carcinoma usually is straightforward, as is the diagnosis of many reactive, inflammatory, and granulomatous disorders. The use of lymph node FNA for the primary diagnosis of malignant lymphoma has proved

more challenging. For this reason, a confirmatory surgical biopsy is done at most hospitals in which a cytologic diagnosis of malignant lymphoma has been made or is suspected. This may not be necessary in selected cases at centers with broad experience in the diagnosis of lymphoproliferative disorders, especially when ancillary marker studies are available to confirm the cytologic interpretation.

One argument for following lymph node FNA with a biopsy is to assess a nodular or diffuse pattern of infiltration, a distinction that carries therapeutic and survival implications based on the grading system enumerated in the National Cancer Institute (NCI) working formulation for non-Hodgkin's lymphomas.

Surgical biopsy must be done in cases of malignant lymphoma of predominantly small cleaved cell type (poorly differentiated lymphocytic lymphoma) and in cases of malignant lymphoma of mixed small cleaved and large cell type. Because these lymphomas show a spectrum of cell size, they may present a diagnostic problem on aspiration biopsy. Furthermore, they are classified as either low-grade or intermediate-grade lymphomas based on the biopsy assessment of a nodular or diffuse pattern. Malignant lymphoma of small lymphocytic cell type (well-differentiated lymphocytic lymphoma), chronic lymphocytic leukemia, and malignant lymphoma of small lymphocytic-plasmacytoid type are low-grade malignant disorders but are difficult to diagnose unequivocally without the benefit of biopsy or ancillary marker studies. On the other hand, a biopsy would not be necessary to grade malignant lymphomas of large cell type, which are classified as intermediate grade whether nodular or diffuse. Large cell malignant lymphoma; malignant lymphoma, immunoblastic (immunoblastic sarcoma); malignant lymphoma, lymphoblastic (convoluted and nonconvoluted T-cell lymphoma); and malignant lymphoma of small noncleaved cells (Burkitt's) are all high-grade lymphomas according to the NCI working formulation and represent lymphomas that can be diagnosed by fine-needle aspiration.

Although centers with expertise in hematologic disorders may not require a confirmatory surgical biopsy in the FNA diagnosis of several types of malignant lymphoma, hospitals that have limited experience in this discipline should continue to use confirmatory surgical biopsy for diagnostic accuracy rather than relying on aspiration cytology alone.

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Biopsy Findings in Liver Transplant Patients

IN THE PAST FEW YEARS, orthotopic liver transplantation has become a relatively common therapy for a wide variety of both pediatric and adult liver diseases. Despite improved surgical and immunosuppressive techniques, patients undergoing this procedure are vulnerable to numerous complications involving transplantation-associated injury to the donor organ, infection exacerbated by immunosuppression, biliary obstruction or leaks, vascular occlusion, and acute and chronic rejection. Liver biopsy has been shown to be an important adjunct to radiologic and serologic studies in these patients and is essential in discriminating between rejection and ischemic injury, two of the most common causes of graft dysfunction, as well as sometimes identifying viral infections in these immunosuppressed patients.

Acute rejection is histologically characterized by a mixed inflammatory infiltrate of the portal tracts composed primarily of T cells but with significant proportions of plasma cells, neutrophils, and eosinophils as well. These inflammatory cells are frequently found intimately associated with the epithelial cells lining the small interlobular bile ductules and the endothelial cells of the portal and centrilobular blood vessels (endotheliitis). This association is believed to be due to the stronger expression of major histocompatibility complex antigens by the bile duct and endothelial cells when compared with the hepatocytes. As a consequence, in most cases of rejection the bile ductules will show evidence of injury or regeneration while hepatocyte necrosis is not a prominent feature. Biliary epithelial injury can occasionally become so severe that most of the ductules will be completely destroyed over a long-term course ("vanishing duct syndrome"), a condition usually requiring retransplantation. Chronic injury to the liver vasculature has also been reported, with arteriolar thickening, fibrointimal hyperplasia of the large arteries, and the accumulation of subintimal foam cells in the hilar vessels with partial occlusion.

Ischemic injury to the liver is the second most common source of acute graft dysfunction and manifests four basic patterns on liver biopsy—focal infarcts, massive centrilobular necrosis, diffuse individual hepatocyte necrosis, and centrilobular hepatocyte ballooning. Focal infarcts occur as a result of ischemia of a specific portion of the liver either perioperatively or from postoperative vascular occlusion. They can vary in size and distribution, histologically showing confluent tissue necrosis with adjacent viable tissue; because of the focal nature of this lesion, a single liver biopsy may not detect it. The clinical sequelae of infarction depend on its extent and whether the necrotic tissue becomes secondarily infected.

Generalized, massive centrilobular necrosis is the result of diffuse liver injury, such as severe hypotension; this histologic finding usually leads to retransplantation. Diffuse, scattered, individual hepatocyte necrosis without inflammation is also a pattern of generalized ischemic injury, and depending on the severity of the insult there may be only a few necrotic cells within the lobule or numerous necrotic cells followed within three days by generalized graft destruction. Less severe generalized ischemic injury results in centrilobular hepatocyte "ballooning" in which liver cells around the central vein become notably swollen, with clear, "hydropic" cytoplasm. In most cases this swelling resolves without sequelae; in severe cases, however, there may be eventual centrilobular hepatocyte loss followed by pronounced cholestasis without apparent duct obstruction.

Viral infection clinically mimicking rejection or ischemia can be detected by biopsy in many cases. The most common virus is cytomegalovirus, but herpesvirus, adenovirus, and hepatitis B virus have also been described. Characteristic viral inclusions or patterns of necrotic hepatocytes in association with inflammatory cells are clues to viral infection. Immunohistochemical stains and DNA hybridization studies

can also be used on the biopsy tissue to detect viral infection.

Although the histologic patterns have been described individually, rejection, ischemia, and viral infections can occur simultaneously, with each contributing to a varying degree to the extent of liver injury.

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The Molecular Pathology of Prion Diseases

NEW PATHOGENETIC MECHANISMS are being discovered for the group of central nervous system (CNS) diseases that includes Creutzfeldt-Jakob disease, the Gerstmann-Straussler syndrome, and kuru in humans and scrapie in animals. These disorders have been grouped together because they have similar clinical, genetic, and histologic features—spongiform degeneration of neurons, astrocytic gliosis, and amyloid plaque formation—and because each is infectious. Originally it was postulated that they were caused by an atypical virus because of the small size of the infectious particle predicted from experimental studies and the absence of histopathologic features characteristic of viral infections. That possibility, however, is now considered unlikely because of studies at the University of California at San Francisco showing that highly purified preparations of the scrapie agent consist almost entirely of a single protein and no detectable nucleic acid. For this reason, the smallest infectious particle was termed a "prion" and the protein associated with infectivity was termed the "prion protein."

Although the structure of the prion and the precise role of the prion protein in infectivity are not known, it has been learned that the prion protein is an abnormal derivative of a normally expressed CNS nerve cell sialoglycolipoprotein. The normal isoform is synthesized continuously in hamster nerve cells, is highly susceptible to proteinase K digestion, and turns over rapidly. In contrast, the abnormal isoform resists proteinase K digestion, turns over slowly, and accumulates in the brain during scrapie. Moreover, the abnormal isoform of the prion protein accumulates precisely in those regions of the gray matter where spongiform degeneration of nerve cell processes and reactive astrocytic gliosis are greatest. It also polymerizes into the filaments that form the amyloid plaques characteristic of these diseases.

Evidence indicates that a human isoform of the scrapie prion protein causes Creutzfeldt-Jakob disease, the Gerstmann-Straussler syndrome, and kuru. Abnormal proteinase-resistant forms of the prion protein, which react specifically with anti-hamster prion protein antibodies, have been found in the brains of patients with Creutzfeldt-Jakob disease but not in normal brains or those of patients with Alzheimer's disease. The amyloid plaques in the brains of patients with Creutzfeldt-Jakob disease and those with the Gerstmann-Straussler syndrome react specifically with anti-hamster scrapie prion protein antibodies. Also, human chromosomes contain a single-copy prion protein gene that has been localized to chromosome 20. In addition, the amino acid sequence of the human prion protein is 90% homologous to the hamster and mouse prion protein. For these reasons, scrapie, Creutzfeldt-Jakob disease, the Gerstmann-Straussler syndrome, and kuru have been grouped under the term "prion disease."

The central pathogenic event in prion diseases appears to be the abnormal metabolism and accumulation of a normally expressed nerve cell protein. The unique feature of prion diseases is that the abnormal prion protein appears to participate in transmitting the disease. The prion hypothesis is consistent with the failure to find a virus and with the absence of an inflammatory or immune response. It is genetically consistent because although most cases of Creutzfeldt-Jakob disease are sporadic, 10% are dominantly inherited, and virtually all cases of the Gerstmann-Straussler syndrome are dominantly inherited. Furthermore, the scrapie incubation time gene is genetically linked to the prion protein gene in mice. Therefore, except for infectivity, most of the features of these diseases are difficult to reconcile with the viral hypothesis.

Prion research is now focused on determining the chemical differences between the normal and abnormal isoforms of the prion protein; whether the abnormal prion protein, either alone or with a cofactor, is the transmissible agent; and the molecular mechanisms by which prions induce disease.

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Polymerase Chain Reaction—A Novel Method for Analyzing Specific DNA Sequences

THE ANALYSIS of DNA is becoming increasingly important in the study and diagnosis of hereditary, neoplastic, and infectious diseases. Often, however, the heterogeneity or small quantity of the sample available can limit the usefulness of conventional techniques. The polymerase chain reaction is a new enzymatic method for selectively replicating a specific nucleic acid sequence up to several hundred nucleotides in length within a complex mixture to facilitate its analysis.

To use the polymerase chain reaction procedure, the DNA sequences flanking the region of interest must be known. Two short oligonucleotide primers complementary to each of the two flanking regions but on opposite DNA strands are synthesized. These primers are added in vast molar excess to the sample DNA, which is then denatured and allowed to anneal to the primers. In the presence of deoxyribonucleoside triphosphates, a thermostable form of bacterial DNA polymerase uses each oligonucleotide as a primer to synthesize a copy of the adjacent DNA strand; each newly synthesized strand then provides a new template for synthesis from the opposite primer. By repeated cycles of denaturation, annealing, and synthesis, the region between the two primers is amplified exponentially. A 220,000-fold amplification of the desired region can be achieved after 20 such cycles; the amplified sequence can then be analyzed by a variety of techniques. Automated instrumentation capable of pro-

cessing many specimens for the polymerase chain reaction has recently become available.

The speed and sensitivity of the reaction procedure offer advantages for both prenatal and microbiologic diagnosis. The method has been applied to the prenatal diagnosis of sickle cell anemia and will find wider application as the genetic defects underlying other familial disorders are identified. It is also capable of detecting minute quantities of viral DNA in clinical specimens even before seroconversion occurs. The polymerase chain reaction has already proved useful in research laboratories for detecting mutations of cellular proto-oncogenes that are thought to play a role in human carcinogenesis; it may soon be used clinically to characterize these mutations in individual patients.

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Fine-Needle Aspiration Biopsy in the Diagnosis of Lymphadenopathy in Persons at Risk for AIDS

LYMPHADENOPATHY is a common finding in the acquired immunodeficiency syndrome (AIDS) and in the AIDS-related complex (ARC). Although this lymphadenopathy usually has a restricted differential diagnosis, it can be difficult to establish the precise cause of the nodal enlargement by history, physical examination, radiographic studies, and laboratory tests.

At the San Francisco General Hospital and Medical Center, we have found fine-needle aspiration (FNA) biopsy to be an accurate, well-tolerated, cost-effective, and useful method to initially evaluate lymphadenopathy in patients with AIDS or ARC. We have done more than 120 FNA biopsies of lymph nodes in such patients.

In our experience, about half the lymph node biopsy specimens in such patients show lymphoid hyperplasia. The other half reveal non-Hodgkin's lymphoma, mycobacterial infection, Kaposi's sarcoma, Hodgkin's disease, and various metastatic tumors. The smears showing lymphoid hyperplasia are characterized by a pleomorphic population of lymphocytes, histiocytes, polymorphonuclear leukocytes, plasma cells, and other lymphoid elements. The smears showing non-Hodgkin's lymphoma are characterized by a monomorphic population of abnormal lymphoid cells; we have further classified these cases as diffuse large cell, large cell immunoblastic, and small noncleaved lymphomas. The smears of patients with mycobacterial infections have consisted of histiocytes with thousands of intracytoplasmic organisms. The smears showing Kaposi's sarcoma have clusters of bland spindle cells not associated with inflammatory elements.

Falsely abnormal results ("false-positives") of FNA biopsies of lymph nodes in this group of patients did not occur in our series, but falsely normal ("false-negatives") results can occur. Possible reasons for false-negative results include sampling errors in lymph nodes with focal disease, taking a biopsy of a benign lymph node in a patient with abnormal nodes elsewhere, and error in microscopic interpretation. Because false-negative FNA biopsies can occur, it is imperative that clinicians using this test realize that a benign result does not entirely rule out involvement of the lymph node by a malignant or infectious process.

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DNA Fingerprinting—Applications for Resolving Medical, Legal, and Criminal Issues

THERE IS NOW a genetic test to determine individual identity. This DNA test or "DNA fingerprinting" holds the same standard of certainty as a set of fingerprints. The test exploits the occurrence of tandem-repetitive regions of DNA—minisatellites—which are scattered throughout the human genome. The minisatellites are highly polymorphic or hypervariable, resulting from unequal exchanges that vary the number of short repeat units in a minisatellite. Researchers at Leicester University, England, isolated three human minisatellite DNA fragments by molecular cloning, each containing tandem repeats of closely related variants of a short consensus sequence. Using these cloned DNA fragments as probes to detect the homologous sequences in the restriction endonuclease-digested human DNA, they discovered DNA banding patterns ("fingerprints") that are completely specific to each person. The estimated frequency of unrelated persons showing the same DNA fingerprint is extremely low—5×10^{-19}—and for siblings to share the same pattern is only 1×10^{-6}.

The possible applications of this test to various fields are immense. It opens up a novel approach in forensic science: bits of tissue, stains of blood, or other body fluids left at the scene of a crime may be used to identify their human source. The test has already been done by the Leicestershire police to identify a murderer in a group of several thousand suspects. A miniscule specimen is sufficient to yield a few micrograms of DNA, material whose stability confers an additional advantage for its use as a marker for identification. The state of California is planning a computerized data bank of DNA fingerprinting information on convicted criminals to facilitate the rapid identification of repeat offenders. The test is also conclusive for all practical purposes in resolving cases of controversial parenthood or other familial relationships. Recently, an immigration case concerning questionable maternity was settled by DNA fingerprinting, permitting the son's emigration to England. Routine DNA fingerprinting by immigration authorities should accelerate the application process and avoid cases of arbitrary judgment by immigration officials.

The test provides an unequivocal criterion for discriminating between monozygotic and dizygotic twins of the same sex at birth, until now a problematic area in genetic studies involving human twins. Other potential medical applications of the test include monitoring engraftment of donor marrow;

ascertaining the source of clinical specimens in cases of mix-up; and, perhaps eventually, with an expanded range of minisatellite probes or appropriately synthesized oligonucleotide probes, examining genetic predispositions for diseases for which suitable markers are lacking.

With dramatic success already shown, there is a growing commercial interest in the test, and, in fact, the Imperial Chemical Industry has opened in the United Kingdom its first laboratory for DNA fingerprinting.

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Lymphocyte Gene Rearrangement Studies in Formalin-Fixed, Paraffin-Embedded Pathology Specimens

THE USE OF RECOMBINANT DNA TECHNOLOGIES to detect clonal rearrangements of immunoglobulin or T-cell receptor genes is becoming an increasingly valuable adjunct to more conventional methods in the diagnosis and assessment of B- or T-cell lymphoproliferative disorders. Until recently this technique depended on the availability of fresh or frozen tissue specimens, limiting its applicability in clinical medicine. We have therefore examined the feasibility of using our previously reported procedure for extracting DNA from formalin-fixed pathology specimens for gene rearrangement studies in such specimens.

We were able to show clonal rearrangement of heavy and light chain immunoglobulin genes in about 75% of blocks of formalin-fixed, paraffin-embedded B-cell lymphoma specimens retrieved from the pathology archives at our institution. The success rate at recovering intact high-molecular-weight DNA varied substantially depending on the hospital center from which the paraffin blocks were obtained. The most common reason for failing to recover high-molecular-weight DNA was the use of suboptimally fixed tissue containing partially autolysed areas. Overfixed material was also unsuitable because the amount of intact DNA recovered decreased with the increasing time of exposure to fixative. Tissues immersed in mercuric chloride-containing fixatives such as Zenker's or B5 were not suitable for gene rearrangement studies.

The best results will, therefore, be obtained with tissues sectioned and fixed in buffered formalin immediately after the surgical procedure and preferably for a period of no longer than 24 hours before being embedded in paraffin. Tissues fixed for as long as five days may still be usable, but the quantities of material recovered would be much smaller. Despite its limitations, this technique increases considerably the number of specimens amenable for gene rearrangement studies and should make this approach more applicable to the clinical evaluation of lymphoproliferative disorders.

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Neuropathology of AIDS Dementia

THE AIDS DEMENTIA COMPLEX (ADC) was recognized two to three years ago as a syndrome of progressive neurologic dysfunction that occurs in a substantial proportion of patients with the acquired immunodeficiency syndrome (AIDS). Patients with AIDS may have neurologic abnormalities as a result of one or more of several types of neuropathologic disorders, including opportunistic infections caused by viruses—such as cytomegalovirus, papovavirus, Herpes simplex and zoster viruses—*Toxoplasma gondii,* and fungi such as *Cryptococcus neoformans,* lymphoproliferative disorders including lymphoma and lymphomatoid granulomatosis, and vascular or anoxic-ischemic lesions. Peripheral neuropathy is also frequently found. Early in the AIDS epidemic, however, it became clear that cerebral dysfunction developed in some patients in the absence of any of these specific causal factors. Instead, postmortem examination of the patients' brains revealed poorly defined inflammatory lesions including scattered microglial nodules and perivascular lymphocytes, and myelin loss with intense astrogliosis within white matter of the centrum semiovale of the cerebral hemispheres. Furthermore, Southern blotting methods, in situ hybridization, immunocytochemistry, and electron microscopy showed the presence of the human immunodeficiency virus (HIV) in the brains of many of these patients. A small but definite subset of patients seropositive for HIV appeared to have "pure" brain involvement by this disease without peripheral or systemic manifestations of the syndrome, apparently reflecting neurotropism of HIV in these patients.

Though the ADC is now a recognized and reasonably defined clinicopathologic disorder, its nosology is by no means clear. Patients with the ADC often appear demented out of proportion to the amount of structural damage in the nervous system, although the observed dementia corresponds to the subcortical type expected in patients with primarily white matter brain damage. Conversely, evidence of HIV infection of brain is seen in neurologically normal patients. Although HIV forms with tropism for the nervous system have emerged, the cell type in the brain most commonly infected by HIV is one with macrophage or microglial markers. Infection of astrocytes has been recorded in a few cases, and there is little evidence for infection of neurons or oligodendrocytes. One hypothesis is that HIV-infected macrophages release a product or toxin that damages adjacent white matter.

The pathologic diagnosis of ADC due to HIV infection of brain is based on fairly subtle criteria. White matter injury may be inconspicuous unless large myelin-stained sections are carefully examined. Astrogliosis is best determined using an immunocytochemical procedure for glial fibrillary acidic protein. Finally, perivascular multinucleated cells—including giant cells—with foamy or granular cytoplasm are generally accepted as a marker for HIV within the nervous system. Commercially available antibodies and probes for HIV can also be used for immunocytochemistry or in situ hybridization. The diagnosis can even be made on brain biopsy, but this must be done with great caution because similar, though not identical, white matter changes without the

presence of multinucleated cells may be seen in cases of progressive multifocal leukoencephalopathy or in reactive brain tissue around a lymphoma or other infectious process.

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Papillomavirus in the Lower Female Genital Tract

HUMAN PAPILLOMAVIRUSES (HPV) are classified as genotypes, using molecular hybridization techniques to determine DNA composition, rather than as serotypes based on structural antigens; each genotype has less than 50% genome homology with the other types. At least 46 types of HPV have been identified, 12 of which are associated with lesions of the female genital tract.

Morphologically, condylomas and cervical and vulvar intraepithelial neoplasia may show koilocytotic atypia; this koilocytosis is associated with the presence of HPV. Virus particles have been found in condylomas by electron microscopy, and immunohistochemistry has localized HPV structural antigens to the nuclei of koilocytes.

A number of hybridization techniques may be used to assess tissues for HPV. Southern blot hybridization, applicable to freshly obtained cells and tissues, is the most sensitive and specific technique and can detect less than one copy of HPV genome per cell. Under high and low stringent assay conditions to vary the closeness of the nucleic acid hybrid match, HPV of known and unspecified types can be detected. Dot blot hybridization is a faster but less specific method. In situ filter hybridization was developed for use with freshly exfoliated cells; it also yields more false-positives than the Southern blot technique. In situ tissue hybridization on paraffin-embedded tissue permits specific HPV-infected cells to be identified and localized. With autographic detection using sulfur 35 or tritium, the sensitivity and specificity are similar to those of Southern blotting; with a biotin label, the sensitivity decreases.

Overall, the Southern blot technique has detected HPV DNA in 80% to 90% of cervical condylomas and intraepithelial neoplasia and in 70% to 95% of invasive cervical carcinomas. Differences exist among HPV genotypes in their distribution in the genital tract and in the severity of their associated lesions. In one study, 54% of cervical biopsy specimens of condyloma and intraepithelial neoplasia grade I were associated with HPV type 6 or 11, 13% with type 16, 18, or 31, and 12% with unspecified types; in 21% no HPV was detectable. In contrast, 68% of biopsy specimens of cervical intraepithelial neoplasia grades II and III were positive for type 16, 18, or 31, 12% for type 6 or 11, and 12% for unspecified types, with no HPV detectable in 8%. Other authors have reported comparable trends.

Thus, HPV types 6 and 11 are generally found in ordinary condylomas, although they have infrequently been identified in squamous carcinomas, predominantly of verrucous pattern. Types 16, 18, 31, 33, 35, and 45 are considered to be of higher oncogenic potential and are found mainly in atypical condylomas, moderate and severe dysplasias, and carcinoma in situ and invasive carcinoma of the cervix and vulva. HPV 16 is the most common HPV type identified in invasive cervical squamous cell carcinoma, while type 18 shows a greater association with adenocarcinoma and adenosquamous carcinoma. Preliminary evidence suggests that a progression from condyloma or cervical intraepithelial neoplasia grade I to cervical intraepithelial neoplasia grade III is associated with type 16 or 18 or a mixed infection including one of these types. More than one HPV type are detected in 10% to 20% of patients with carcinoma in situ. Various HPV genotypes, including types 16 and 18, have been detected in 11% of women with normal smears from cervical screening.

There are differences in the physical state of the viral DNA in benign and malignant lesions. Viral DNA is present as extrachromosomal episomes in most preinvasive lesions. Integrated HPV DNA has been noted in dysplasias, invasive carcinomas, their metastases, and cell lines derived from cervical carcinomas.

These findings show important differences among HPV genotypes and strongly suggest that some types of HPV may play a role in carcinogenesis in the lower female genital tract.

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Using the Polymerase Chain Reaction in Detecting Infectious Agents

THE DIAGNOSIS OF INFECTIOUS DISEASES is an important function of pathologists. Because most microorganisms are difficult or impossible to detect or because they speciate on histologic examination, a definitive diagnosis usually depends on culturing. This, however, can be an expensive and time-consuming process, and methods for culturing certain microorganisms are not available. Furthermore, fresh tissue is needed.

In 1985 a new technique of DNA amplification, known as the polymerase chain reaction, was described. With this method, any DNA fragment of known sequence can be selectively amplified and subsequently determined by either dot or liquid hybridization. The DNA does not have to be purified and can even be directly obtained from deparaffinized, thick sections of formalin-fixed, paraffin-embedded material. Therefore, the presence of any infectious agent in tissue or body fluid can be established with sensitivity and specificity, provided that a portion of its DNA sequence is known. This method has been successfully applied to the identification of the human immunodeficiency virus in blood and the human papillomavirus in cervical carcinoma specimens.

The method as described above, however, still involves hybridization using probes labeled with phosphorus 32; therefore, it is not suitable for routine clinical use. Recently the procedure has been improved to the extent that the amplified DNA product can be directly shown as a visible band on an agarose gel after electrophoresis and staining with ethidium bromide. We have successfully used this protocol to

identify hepatitis B virus in serum specimens and herpesvirus in paraffin blocks of specimens of infected skin, with 100% sensitivity and specificity. With this modified technique, the entire procedure can be done in less than six hours, with no need for radioisotopes. Therefore, the polymerase chain reaction offers a rapid, sensitive, and specific technique for detecting infectious agents that can use both fresh and fixed material and in the future may be increasingly used in clinical laboratories for diagnostic purposes.

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Diagnosis of Small Round Cell Tumors in Children

THE TERM "SMALL, ROUND, BLUE CELL TUMORS" refers collectively to a group of several aggressive malignant disorders of childhood of diverse histogenesis that are capable of presenting histologically as proliferations of small primitive cells with round nuclei and undifferentiated cytoplasm. The most important of these are lymphoma, Ewing's sarcoma, rhabdomyosarcoma, and neuroblastoma, although a number of other disorders are occasionally considered in the differential. While most cases of each of these neoplasms can be diagnosed by conventional histopathology, some of these tumors elude identification by routine light microscopy alone. Fortunately, several ancillary techniques, including sophisticated applications of recent advances in immunology, genetics, and molecular biology, are available for resolving problematic cases.

Electron microscopy will often provide an answer in these cases by revealing neuritic processes in neuroblastoma, actin-myosin bundles in rhabdomyosarcoma, glycogen pools and a general lack of cytoplasmic differentiation in Ewing's sarcoma, an absence of true cell attachments in lymphoma, and various other features. Immunocytochemistry has proved its value in the diagnosis of small, round, blue cell tumors. The detection of myoglobin or desmin or both in primitive tumor cells may confirm the diagnosis of rhabdomyosarcoma, while a positive reaction for neuron-specific enolase may point towards neuroblastoma or other primitive neural tumors. Newer monoclonal antibodies against muscle-specific actin and various neural antigens such as Leu-7 and HSAN 1.2 are providing additional help. The demonstration of leukocyte-common antigen may be invaluable in the diagnosis of lymphoma in an unusual site, while a battery of more specific markers may aid in its precise classification.

The most exciting recent advances in the diagnosis of small, round, blue cell tumors have been in the study of tumor cell chromosomes and DNA by cytogenetic and molecular genetic methods. Specific chromosomal abnormalities have been found in certain tumors, such as a reciprocal 11:22 translocation in Ewing's sarcoma. The finding of the same translocation in peripheral neuroepithelioma raises fascinating histogenetic possibilities. Studies of oncogene amplification and expression in small, round, blue cell tumors, such as the N-*myc* oncogene in neuroblastoma, have been shown to provide useful diagnostic and prognostic information and to shed light on tumorigenesis. These and other newer developments bring us closer to our goal of a precise diagnosis in every case of small, round, blue cell tumor.

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Editorials

A Different View of Costs

HEALTH CARE COSTS are very much in the public consciousness, particularly among those who are paying the bills. And, naturally, those who are paying the bills are looking for ways to reduce these costs in any way they can. One approach has been to arbitrarily reduce payments for services. More substantive efforts have been to curtail the kinds and amounts of services that will be paid for in various programs and to introduce incentives that bring less care to fewer people. And then it has been discovered that it does not make sense to provide care for people who do not or cannot pay for it. The result has been that many who may need more or better care are often receiving less. Already there is convincing evidence that health is actually deteriorating among some of the medically underserved segments of the population. Physicians, rather than being acclaimed for the success of their professional achievements in health care, are blamed for much of what is happening, and in their practices they now often find themselves being second-guessed in their professional decisions by persons whose professional responsibility is primarily cost containment. This has been a stressful situation, to say the least.

If one probes a little deeper, it may turn out that the problems of health care are simply the tip of an iceberg of fundamental changes that have begun to occur in what is sometimes called postindustrial America. Similar changes may soon emerge in other highly developed nations, if this is not happening already. The cause is, no doubt, the unprecedented growth of modern science and technology and their subsequent impact on almost every social, economic, and political human endeavor. It is inherent in this burgeoning science and technology that it leads to specialization, and a necessary corollary of specialization is a new interdependence among the specialists, whether they be animate human specialists or inanimate technologic instruments or machines. This pervasive interdependence, in turn, requires additional systems of communication and coordination among many specialized systems if things are to work well, or even at all. It follows that all this complexity of specialization, interdependence, communication, and coordination brings new and inescapable systemic costs, and these are proving to be substantial. In some situations, at least, they are now considered unacceptable.

Certainly, this is happening in medicine and health care where there have obviously been new dimensions of growth in science and technology and in the subsequent costs of applying this new knowledge in all the professional, social, economic, and political arenas of health care. One can begin to see the same thing happening in other parts of our society—and for many of the same reasons. For example, we are facing costly gridlock on our highways. For some time we have been subsidizing farming because farmers could not meet the rising costs of a technologic age. Our educational system has begun to falter because of rising costs that have outrun resources. And our legal system may yet turn out to be the most costly of all. Like the others, it is ill adapted to deal with the rapidity of change in this age of burgeoning science and technology, with the as yet poorly understood complexity and interdependence that result. Unfortunately, the legal system, as it now operates, also adds significantly to the costs incurred by many other segments of society. There are many other examples.

All of this suggests that there may need to be a different view of costs. Rising costs may simply be an inevitable result of new dimensions of growth that are occurring in the more advanced societies that are undergoing what amounts to a technologic revolution. The costs of specialization and the consequent interdependence among specialties and specialists, animate and inanimate, and all that this entails, are no more likely to go away than are new science and technology. Nor are they likely to be controlled by any conventional means. We live in a new era where there is what amounts to an iceberg of fundamental change, not yet recognized for what it is, and health care, for better or worse, is at the tip of this iceberg. This writer's crystal ball is murky about what lies ahead, but scientific and technologic progress will continue and must be made to work for the betterment and well being of humans. So the professional, social, economic, and political systems of modern postindustrial societies must somehow adapt. There will need to be new rules and new ways of doing things. Health care is out in front and health care is what the medical profession is all about. Perhaps it is time for a new dimension of growth for the profession of medicine that will match the new era of social, economic, and political growth in society as a whole that will be brought about by this era of fundamental change that is bursting upon us as a result of modern science and technology. Could the traditional role of physician to patient somehow grow into a new role for the medical profession as physician to society? The profession might take a different approach that might lead to a different view of costs. Health care costs can be studied anew. It just might be worth thinking about.

MSMW

Leadership in the West

SOMETHING IS WRONG when 30 or 40 million Americans are said to be without any health insurance and therefore are denied the access to health care resources that is enjoyed by most Americans. No doubt for some this is a matter of their choice. But for others, particularly for those who are employed and yet have no insurance, it has to be said that the system has not been working very well. So far, no one has come forward with a workable solution for this problem.

Physicians who attempt to care for patients who get sick and have no health insurance are closer to this unmet need than most. Patients who are gainfully employed but nevertheless uninsured for their health care are no rarity in many physicians' practices. Individual physicians find themselves relatively powerless to deal with this situation, particularly when the requirements for adequate care are beyond their own capability to render services, whether at reduced rates or pro bono. Adequate health care usually requires much more than just a physician's services.

Physicians in the aggregate, through their medical associations, can be effective in many ways that individual physicians cannot. With their combined strength they might find opportunities to collaborate with others who are also prop-

erly concerned with finding some kind of reasonable and feasible solution, at least for the medically uninsured who are gainfully employed but still have no health insurance. The leadership of the California Medical Association has just embarked on a program to develop a coalition of groups and organizations interested in finding ways to make health insurance available to persons who are employed but who, along with their families, are uninsured for health care under the present system. This is an imaginative grass roots approach, calling upon the many interested parties to work together to find ways to solve a common problem. If successful, it should be yet another example of leadership from the West in matters of health care.

MSMW

Case Reports

IUD Appendicitis During Pregnancy

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AN INTRA-ABDOMINAL INTRAUTERINE DEVICE (IUD) was found during an appendectomy in a 29-year-old woman who was 20 weeks pregnant. The IUD had apparently been lost about seven years previously, when she became pregnant shortly after it was inserted. Abdominal and pelvic x-ray films during the third trimester of that pregnancy were interpreted as normal, and she went on to have a normal vaginal delivery. Appendicitis developed at 20 weeks' estimated gestational age with the next pregnancy seven years later.

Report of a Case

The patient, a 29-year-old woman—gravida 4, para 3, living children 3—whose last menstrual period was October 20, 1986, had an ultrasound study done in mid-April 1987 because of poor size-dates correlation; from the results, the expected date of confinement was determined to be August 29, 1987. On the morning of admission, right lower quadrant pain developed that became progressively worse and was associated with nausea, anorexia, and fever and chills. On abdominal examination she had good bowel sounds. She had pain referred from all areas of her right lower quadrant, centered just above McBurney's point. She had minimal guarding but dramatic rebound tenderness and a positive right psoas sign. The uterine fundus was at the umbilicus, and the fetal heart tones were 150 beats per minute. On rectal examination she was tender along the right posterior pelvic wall. A pelvic examination showed no abnormalities. Her leukocyte count on admission was 16,400 per μl.

At laparotomy, the cecum and appendix were both noted to be bound down inferior and posterior to an inflammatory mass that also involved the inferior portion of the broad ligament and the sigmoid colon. The right tube and ovary were free of involvement. The tip of the appendix was gently freed from the mass, and an appendectomy was done. A small whitish blue string was noted protruding superiorly out of the mass, and, with gentle traction, the string was partially exposed and identified as the tail of an IUD. The IUD was then removed with blunt dissection and gentle traction, and it was noted to be copper-coated. A culture of the IUD eventually grew *Escherichia coli,* but peritoneal cultures failed to grow any bacteria. A Penrose drain was left in the pelvic gutter, and the abdomen was closed. The patient had an uneventful recovery on a regimen of intravenous cefoxitin (Mefoxin).

Discussion with the patient after the operation revealed that she had an IUD placed about eight years before admission, at which time she had had moderate right lower quadrant pain. The pain quickly resolved, but she continued to have intermittent, low-grade right lower quadrant pain. About five months after placement, she had an episode of severe right lower quadrant pain; she went to an emergency department and was found to be pregnant. The results of a vaginal examination at the time and abdominal and pelvic x-ray films at nine months of gestation were thought to be consistent with an expelled IUD (Figure 1). That pregnancy resulted in an uncomplicated vaginal delivery in March of 1980. During the past seven years, she had continued to have episodic right lower quadrant pain of mild to moderate severity.

After the appendectomy, she went on to have a normal prenatal course, but after induction for postconfinement dates failed, she required a primary, low-transverse cesarean section. At cesarean section, dense adhesions were noted between the right posterior side of the uterus and the posterior pelvic wall. Dense adhesions also involved the right broad ligament, right ovary, and the right fallopian tube. The previous inflammatory mass was not palpable at this time. Recovery from the cesarean section was uneventful.

Pathologic Findings

On microscopic examination of the appendix, the full thickness of the wall was infiltrated with sheets of neutrophils. No fecaliths were noted in the appendix.

Discussion

The disappearance of an IUD may be due to either tail retraction, expulsion, or perforation. Any missing IUD should be aggressively sought, even if lost within the first year. It is estimated that the rate of expulsion is 2% to 20% within the first year and especially the first three months.[1] Expulsion and perforation seem to be more common after either an abortion or delivery.[1] The basic workup for a missing IUD includes abdominal radiographs, ultrasonography, or contrast hysterography.

The incidence of uterine perforation has been reported as somewhere in the range of 1 per 350 to 1 per 2,500.[2] The cause of perforation is probably a combination of traumatic insertion and erosion of the device through the uterine wall. Complications of perforation include either chronic or acute inflammation or penetration of a hollow viscus, such as the bladder with subsequent stone formation, the small intestine with the development of small bowel obstruction, and the large intestine. The estimated incidence of these types of complications after perforation is as high as 15%.[3]

The penetration of hollow viscera is facilitated by at least one of three mechanisms: primary penetration, migration, or inflammation.[4] Primary penetration may occur when the IUD is traumatically inserted through the uterine wall into an organ juxtaposed to the uterus. Migration to an adjacent organ may occur through facilitation by the omentum or by an enlarging pregnant uterus. Inflammation plays an important role in the pathogenesis of penetration because most documented cases involved devices that contained copper, which is inflammatory.[4-8]

The present case illustrates several interesting points con-

(McLaughlin DI, Bevins W, Karas BK, et al: IUD appendicitis during pregnancy. West J Med 1988 Nov; 149:601-602)

From the Billings Clinic, Red Lodge, Montana.
Reprints are not available.

Figure 1.—A pelvic x-ray film taken in March 1980 shows a gravid uterus at term and an intrauterine device in the right pelvic area.

cerning uterine penetration by an IUD. First, an initial workup with a plain film of the abdomen was misinterpreted and the intra-abdominal position of the IUD missed. This was probably due to a near-term gravid uterus. Second, the point when complete uterine perforation occurred is unknown, but it was presumably before her third child was conceived. Her uterus was most likely partially perforated with insertion of the device, and over the following two to three months complete perforation occurred. The periodic pain she experienced after that pregnancy was probably related to episodic exacerbation of chronic, low-grade inflammation in the mass surrounding the IUD. Third, as the gravid uterus grew, the inflammation surrounding the IUD eventually involved the appendix, and acute appendicitis developed. Finally, reexamination of the pelvis at cesarean section showed that the inflammatory mass had been replaced with dense adhesions that now included the right adnexa, which had previously been free of the pathologic process.

Summary

This case shows that abdominal and pelvic x-ray examinations may not adequately show a misplaced IUD in a gravid woman, and further workup is necessary after delivery if the IUD is not clearly visible on the initial x-ray films. It also shows that chronic inflammation may develop in the area of a misplaced IUD, producing chronic abdominal pain and complications, even after several years have transpired. Finally, patients may still be at risk for complications after an IUD has been removed because of the dense adhesions that develop due to the chronic inflammatory response elicited by the IUD.

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Diabetic Ketoacidosis Following Pentamidine Therapy in a Patient With the Acquired Immunodeficiency Syndrome

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GLUCOSE INTOLERANCE and insulin-requiring diabetes mellitus are well-described complications of pentamidine therapy that often follow episodes of hypoglycemia occurring during the use of the drug. These disorders are due to a direct cytotoxic effect of pentamidine on insulin-producing pancreatic β-cells. Searching the literature, we found only one reported case, appearing as an abstract, of ketoacidosis associated with pentamidine-induced diabetes mellitus, despite its now frequent use to treat *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). Herein we report the case of a patient with insulin-requiring diabetes mellitus due to pentamidine therapy in whom increased insulin requirements developed and who had diabetic ketoacidosis following treatment with pentamidine of a second episode of *P carinii* pneumonia.

Report of a Case

The patient, a 42-year-old male homosexual, was admitted in October 1986 with fever, dyspnea, and interstitial infiltrates on chest films. The patient had no history of diabetes mellitus, and his fasting serum glucose level on admission was 5.7 mmol per liter (102 mg per dl). Bronchoscopy showed *P carinii,* confirming the clinical suspicion of AIDS, and a regimen of trimethoprim-sulfamethoxazole was started. The patient responded to therapy, but a pruritic drug eruption developed, and his therapy was switched to pentamidine isethionate, 4 mg per kg body weight for 15 days. On day 5 of pentamidine treatment, hypoglycemia developed, with serum glucose values between 2.2 and 2.8 mmol per liter (40 and 50 mg per dl). The patient subsequently had

(Lambertus MW, Murthy AR, Nagami P, et al: Diabetic ketoacidosis following pentamidine therapy in a patient with the acquired immunodeficiency syndrome. West J Med 1988 Nov; 149:602-604

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hyperglycemia on day 12 with the serum glucose level rising to 19.4 mmol per liter (350 mg per dl). Insulin was required for adequate control.

The patient did well for eight months, with stable glucose determinations on a regimen of 28 units of NPH insulin daily. He also received zidovudine (Retrovir), 200 mg every four hours, since November 1986. The patient was readmitted in June 1987 with recurrent *P carinii* pneumonia and was again treated with pentamidine isethionate, 4 mg per kg given intravenously daily. The patient also received intravenous glucocorticoids for three days—120 mg of methylprednisolone sodium succinate daily—for worsening respiratory insufficiency, but ultimately had resolution of his pulmonary infection. His glucose control worsened significantly during the pentamidine treatment, despite cessation of the glucocorticoid therapy, necessitating doubling of his daily insulin dose at discharge (Figure 1). The patient had received no steroids the preceding ten days before discharge.

Following discharge, the patient omitted his evening and morning insulin doses, and subsequently anorexia, polyuria, and polydipsia developed. His condition worsened, and he was readmitted 36 hours after being discharged. The patient was acutely ill with Kussmaul's respirations and dehydration, but there was no evidence of infection on physical examination. The serum glucose level was 64.4 mmol per liter (1,160 mg per dl), and the serum bicarbonate concentration was 10 mmol per liter. Serum acetone was present at a dilution of 1:8. A urinalysis revealed 4+ glucose and 3+ ketones. Blood cultures showed no growth.

The patient was treated with an insulin infusion with rapid control of the serum glucose level and resolution of the ketoacidosis. The patient spiked a fever to 39.4°C (103°F) on the third hospital day, and blood cultures were subsequently positive for *Listeria monocytogenes.* An analysis of cerebrospinal fluid showed no abnormalities. Because of penicillin and sulfa allergies, the patient was treated with a regimen of intravenous followed by oral erythromycin and did well. He was discharged on a total daily dose of 70 units NPH insulin.

Comment

The use of pentamidine in the treatment of protozoan infections, including *P carinii* pneumonia in patients with AIDS, is associated with serum glucose abnormalities. Hypoglycemia has been noted in 6% to 10% of patients during or soon after therapy.[1-4] Actual incidence rates may be higher due to asymptomatic hypoglycemic episodes that go undetected. Glucose intolerance and overt diabetes mellitus have occurred following pentamidine therapy in as many as 5% of patients, usually after completion of treatment and often following episodes of hypoglycemia.[3,4,5] Asymptomatic hypoglycemia developed in our patient at day 5 of therapy, with the onset of insulin-requiring diabetes mellitus at day 12 during his initial treatment of *Pneumocystis* infection.

The biphasic response of serum glucose is caused by a direct cytotoxic effect of pentamidine on pancreatic β-cells similar to the action of streptozocin.[4,7] This effect has been shown in vitro to be dose related and dependent on the duration of exposure. The initial hypoglycemic episodes are characterized by increased serum levels of insulin released during cytolysis of the β-cells. If destruction is widespread, a relative state of insulin deficiency is induced with glucose intolerance or diabetes mellitus.[4,5,7] Diazoxide has been shown to correct pentamidine-induced hypoglycemia[8] but not to prevent subsequent diabetes in one patient.[5] The relative safety of pentamidine therapy in patients with diabetes mellitus has been touted,[5,9] although one case of ketoacidosis following pentamidine therapy has been reported in abstract form.[10]

Insulin-requiring diabetes mellitus developed in our patient following treatment of *P carinii* pneumonia. During retreatment with pentamidine eight months later, the patient had worsening hyperglycemia and increased insulin requirements, presumably due to the destruction of remaining β-cells. The occurrence of ketoacidosis following noncompliance with his insulin therapy and during acute infection further confirms that a continued depletion of pancreatic islet cells responsible for insulin production results in diabetes

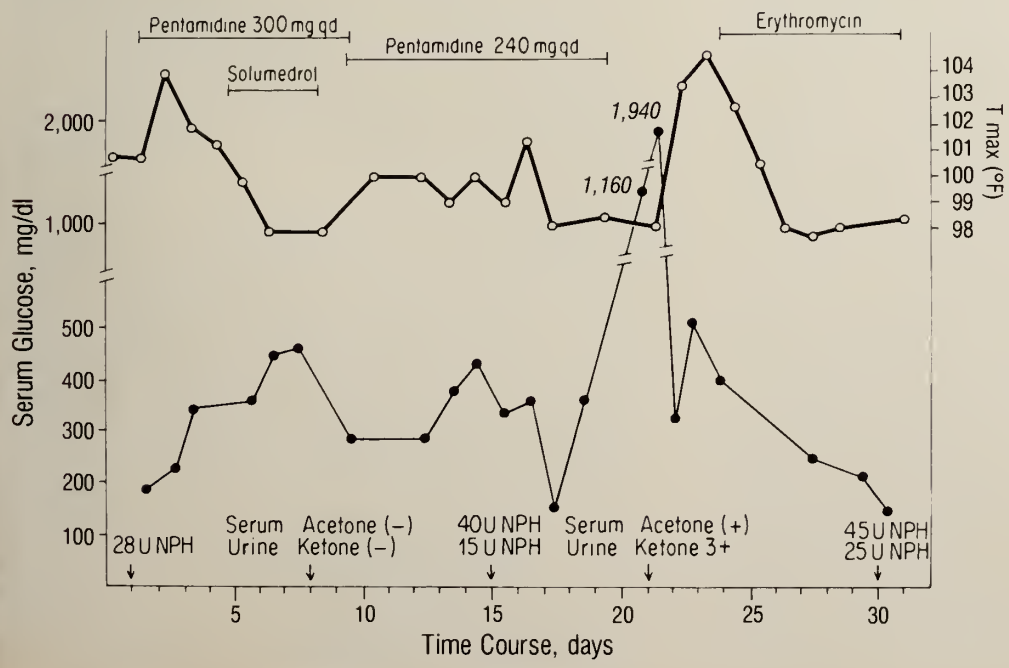

Figure 1.—The graph shows the relation of patient's serum glucose levels (●) to pentamidine isethionate therapy, steroid administration, fever (○), and *Listeria monocytogenes* septicemia. AM (upper) and PM (lower) NPH insulin doses are also displayed.

mellitus type I. *L monocytogenes* sepsis followed the resolution of acidosis, and while occult infection may have aggravated the hyperglycemia, it is apparent that the acidosis was ketotic and not due to lactic acid occurring with infection.

We report this case to highlight the potential risk of retreatment with pentamidine in patients in whom diabetes mellitus has developed due to initial therapy. Continued β-cell toxicity does occur, and serious complications, including diabetic ketoacidosis, may result, as shown both by our patient and the previously reported case. Though not supported by case reports, there would appear to be a theoretic hazard in treating persons with diabetes mellitus unrelated to pentamidine administration. Patients with insulin-dependent diabetes would appear to be at particular risk. As pancreatic β-cell toxicity is dose related in vitro[4,5] and in vivo,[10] renal insufficiency may increase the likelihood of pancreatic toxicity. Our patient had transient creatinine elevations during pentamidine therapy due to glycosuria and dehydration that may have resulted in increased drug levels. Various adjuvant therapies, such as diazoxide and corticosteroids, do not prevent diabetic sequelae of pentamidine therapy,[5] as our case shows, the patient having received glucocorticoids early in treatment. The advent of newer treatment modalities, including aerosolized pentamidine or reduced intravenous dosing, may allow a reduction in drug toxicity and the prevention of complications, including pentamidine-induced glucose abnormalities.[11]

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Correspondence

Rattlesnake Meat Ingestion—A Common Hispanic Folk Remedy

To the Editor: A recent article on rattlesnake capsule-associated *Salmonella arizona* infections in Los Angeles emphasized the importance of being aware of the potentially dangerous Mexican folk remedy of ingesting rattlesnake meat.[1] The authors suggested that the use of rattlesnake capsules by the Hispanic population in areas of the United States with large Mexican-American populations is probably widespread. We recently conducted a survey to determine the extent of use and knowledge of the folk remedy of rattlesnake meat ingestion and the reasons given for its use. Patients were interviewed from R.E. Thomason General Hospital, the county hospital serving the indigent population of El Paso, Texas, situated on the US-Mexican border across the river from Ciudad Juarez.

A standardized, orally administered, open-ended questionnaire in English or Spanish was given to 200 consecutive outpatients seen in the medicine clinic. Patients were asked if they knew of the folk remedy of ingesting rattlesnake meat, powder, or capsule; if so, the reason(s) people use it; and if they or a close family member had ever used this remedy. Statistical analysis for differences between proportions was done by the χ^2 test with 2×2 contingency tables.

All 200 patients interviewed responded. There were 132 men and 68 women, ages 17 to 83 years (mean 52.8). Of these, 177 (88.5%) were Hispanic. A total of 156 of the 200 patients (78%) had heard about the folk remedy of ingesting rattlesnake meat to treat illnesses. These represented 82% (146/177) of Hispanic patients and 43% (10/23) of non-Hispanic patients ($P<.001$). Of the 200 patients, 67 (33.5%) said that either they or their relatives had used rattlesnake remedies to treat illnesses. Of these, 37% (66/177) were Hispanic and only 4.3% (1/23) were not ($P<.005$). The illnesses cited most frequently for which rattlesnake meat ingestion was helpful were skin conditions, 53 patients (34%); arthritis, 30 (19%); stomach problems, 22 (14%); blood diseases, 21 (13%); cancer, 19 (12%); infections, 18 (12%); diabetes mellitus, 18 (12%); hypertension, 7 (4%); "nervous conditions," 5 (3%); allergies, 4 (3%); and miscellaneous illnesses, 20 (13%). Additionally, 4 patients thought it would improve their strength, and 2 took it because it tasted good.

Results of our survey in El Paso are consistent with the conclusion that the folk remedy of ingesting rattlesnake meat is well known among the Mexican-American population and that it is commonly used in some areas for a variety of indications. Physicians should be aware of their patients' cultural beliefs and possible use of folk remedies, either instead of or in addition to standard medical treatments.[2,3] In view of the risk of serious salmonella infections, we concur with the authors' suggestion that education is needed regarding the potentially harmful consequences of this particular folk remedy.

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Acknowledgements

To the Editor: I would like to acknowledge two important contributors to my article, "Arsenic Poisoning," which appeared in the September issue of the journal.[1]

This was a clinical conference, and the pathologic material I presented was graciously provided by Karen Blisard, MD, and Patrick Lantz, MD. Dr Blisard, a neuropathologist at the Albuquerque Veterans Administration Medical Center, supplied the osmium stained sections of nerve tissue shown in Figure 7. Dr Lantz, a pathologist at the Albuquerque Office of Medical Investigation, supplied the autopsy material presented in Figures 4 and 5. Both of these investigators have scholarly works in press on the pathologic effects of arsenic, and I am grateful for the early use of their material in my article.

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Yellowstone as Metaphor

To the Editor: There is an almost spiritual similarity between our public grieving over the fire damage in Yellowstone Park and our almost obsessive desire to preserve human life for as long as possible.

Naturalists and ecologists seem to agree that our national emotional reaction to the fire devastation in Yellowstone Park is out of proportion to the actual damage to the ecosystem. It has been pointed out by some less frenetic scientists and journalists that the true treasures of that park are its hydrothermal pools, its geysers and animals, and its emotional meaning to us as the first and "grandest" of our national parks. It was, after all, conceived and founded by a popular president—good old Teddy Roosevelt—and ranks in national pride somewhere between Old Ironsides and the flag over Fort Sumter . . . and yet someone deliberately decided to let half of it burn up. There is a nagging suspicion that some of the grief and sensation over the burn may have been inspired by economic concerns—it was, after all, a very visual television story during the news doldrums between the end of the Gulf war and Hurricane Gilbert.

One senses an eerie similarity in our perception of loss of the park and our inability to come to grips with the finality of the human life cycle—our collective need to preserve life, almost any life, indefinitely and almost without any regard for the quality of that life. For us, as physicians whose lives are dedicated to staving off that finality as long as possible, empathy is understandable because to us death is defeat. People are born programmed to die, but our national psyche seems to have lost touch with its own inevitable mortality.

Perhaps just as it was impossible for the National Park

Service to know when natural and cleansing forces from fire were turning to unnatural disaster, if indeed they ever were, it is difficult for humans to know when to stand back and let the tides of fate preside over our mortality.

Even as we wring our hands over the scars of the burning of thousands of acres of spindly, really not so beautiful lodgepole pines, we must remember that Old Faithful and all the geysers will still erupt on the same schedule, the falls in the flow of the Yellowstone River will continue, the reflections on the lake will still sparkle in the sunset, and even the historic and hoary Old Faithful Lodge will remain to welcome us. The park will be there for our children and our grandchildren. The folks we entrusted to preserve our national wonders did not fail us.

This conflagration may be seen as a disaster or as a spiritual metaphor for us in grasping our own mortality. I do not expect the people who live in the park to accept the loss of their homes and their surroundings with total equanimity—they are much too close. I do not expect the relatives of the very sick and dying to be any more philosophical. But as a civilization there must be a lesson for us in observing the natural ebb and flow of nature in what has just happened to our oldest national park.

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Cancer Patients and Sperm Banking

To THE EDITOR: Today, many patients are surviving leukemia and cancer treatments and going on to live normal, productive lives. A part of that new life for some patients is the desire to have children. Unfortunately, chemotherapy and radiation leave most men sterile; yet, there is a way for these patients to still have their own children—through sperm banking.

This subject is not being discussed with the patient and his family often enough—in fact, almost never. Some patients, because of the progression of their disease, are unable to store sperm, but many are able and do have the time to delay treatment in order to store sperm.

Please help me get this message to physicians. Having something to hope for can give the patient the will to live that truly can make all the difference. My husband was one of the lucky ones. Even though I was told to think about funeral arrangements, Dave survived, and today we are the proud parents of the first child born to a Fred Hutchinson Cancer Research Center leukemia patient who stored sperm! Our story is one of hope and joy. Maybe it is about time the successes are shared.

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Prevention Is the Answer

To THE EDITOR: The editorial in the May 1988 issue of the journal[1]—"Can Any Good Come From AIDS?"—merits some observations. You point out that the disease is lethal, it is spreading, and yet there has been no *scientific* way to prevent or cure it.

The acquired immunodeficiency syndrome (AIDS) needs to be considered in perspective. That it is indeed a terrible and devastating disease, no one can deny. Since AIDS was discovered, however, we have documented fewer than 40,000 deaths in the United States, and we are concerned that we may be having over 50,000 deaths a year by the early 1990s. That is indeed a tragedy. Why are we not equally as concerned that before this year ends we will have had nearly 140,000 deaths from lung cancer, mostly from cigarette smoking? Why are we not equally as concerned about the thousands of people who are killed and maimed by drunk drivers each year? Why are we not equally as concerned about the 1,000 people who die before their time every day in this country just from smoking cigarettes?

Half of all deaths in this country are from a single pathological process—atherosclerosis, the underlying cause of most heart attacks and strokes. Nearly a fourth now die of cancer. There is overwhelming evidence that both of these major problems are highly related to poor life-style choices or eating habits.

There is great concern over the increasing cost of health care. Currently, most of our emphasis in medicine is on what we would call crisis medicine—diagnosing and treating established disease. I cannot think of any disease that has been conquered with diagnosis and treatment. As long as we do nothing to slow down the flow of sick people, we will continue to find ever more sophisticated and expensive means of diagnosing and treating their diseases.

Prevention is the answer to the high cost of medical care. This will require massive education of the public to help them make appropriate life-style and dietary choices.

One of the good things that may come out of AIDS is the massive public media attention to the fact that prevention is the answer not only to AIDS but to cardiovascular disease, cancer, and many other diseases that afflict our population.

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Of Surgeons and Football Players

To THE EDITOR: Surgeons are to medical practice what professional football players are to sports. The main difference in the two is that pro football players must please millions of viewers, whereas surgeons are responsible to only one. Nevertheless, both have a right to a level playing field.

The requirement that patients be admitted to hospital the day of a major operation causes a tilt of the field against the surgeon comparable to a football rule that prohibits a huddle throughout a game.

The liability imposed on surgeons by not allowing them time to get the operative act together is comparable to the football player being assessed $100,000 for each dropped pass.

Pro football players and surgeons do not part company even when it comes to the bottom line: a good result is not just the best thing, it is the *only* thing.

Efforts of chiefs of surgery and administrators to make surgeons comply with unreasonable constraints are downright immoral. This is no time to improve the bricks and mortar of the gas ovens—it is time to refuse to comply.

Vice President Bush wants a kinder and gentler nation. Physicians have been in favor of that idea for centuries, so it is time the government freed them up to let them make good on that ideal again.

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Topics in Primary Care Medicine

Olecranon and Prepatellar Bursitis

Diagnosis and Treatment

JOHN H. McAFEE, MD, *and* DAVID L. SMITH, MD, *Portland*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

A bursa is a synovial pouch that reduces friction between adjacent tissues. More than 150 bursae have been identified in the human body. Of these, the olecranon and prepatellar bursae are particularly predisposed to infection and inflammation. In this article, we briefly review the anatomy of the olecranon and prepatellar bursae and discuss the clinical features and treatment of both septic and nonseptic bursitis.

Anatomy and Incidence

The olecranon bursa is the only bursa of the elbow joint. It is positioned subcutaneously on the extensor aspect of the elbow over the olecranon process of the ulna. The bursal anatomy of the knee is more complex, with four bursae recognized over the extensor aspect of the knee joint (Figure 1). The suprapatellar bursa located between the femur and quadriceps tendon communicates with the knee joint as an extension of that synovial cavity. The deep infrapatellar bursa lies between the patellar ligament and proximal tibia and rarely becomes symptomatic. The subcutaneous infrapatellar bursa is positioned between the skin and tibial tuberosity, and the prepatellar bursa is between the skin and patella. Though anatomically distinct, the prepatellar and subcutaneous infrapatellar bursae are affected by similar processes and are collectively referred to as the "prepatellar" bursa. The olecranon and prepatellar bursae are closed spaces that ordinarily do not communicate with the associated joint space.

The incidence of olecranon and prepatellar bursitis is not known. Several articles suggest that septic olecranon and prepatellar bursitis account for between 0.01% and 0.1% of hospital admissions. The overall incidence of olecranon and prepatellar bursitis is probably underestimated by these hospital-based studies because only about 30% of cases are septic, and only patients with the most severe cases of septic bursitis require admission.

The approach to diagnosing olecranon and prepatellar bursitis is to broadly classify the condition as septic or nonseptic. Nonseptic bursitis is further categorized as idiopathic, traumatic, or crystal-induced.

Features of the Condition

Septic Bursitis

Septic bursitis usually arises from trauma resulting in direct inoculation of the bursal space. Blunt trauma, a skin wound, or repetitive pressure applied over the knee or elbow may precipitate an infection. Septic bursitis arising from infection in nearby sites, such as in cases of paronychia, has also been reported. In contrast, hematogenous bacterial seeding of the bursal sac is rare, probably because of the limited vascular supply of the bursal tissue.

The population at risk for the development of septic bursitis includes laborers such as miners, gardeners, carpet layers, and mechanics, in whom repetitive knee or elbow trauma is common. Those with a history of alcoholism are also prone to septic bursitis due to the repeated traumas they receive while intoxicated, coupled with their impaired host immunity. Likewise, septic bursitis has developed in some patients with impaired host defense due to the use of systemic glucocorticoids or to certain medical conditions such as malignancy, leukopenia, diabetes mellitus, or chronic renal failure. The presence of intrabursal rheumatoid nodules or gouty tophi, or a prior history of septic bursitis increases a person's risk of bursal infection. Iatrogenic sepsis may follow an intrabursal steroid injection for nonseptic bursitis.

Nonseptic Bursitis

Traumatic and idiopathic bursitis likely have a common origin, and idiopathic cases result from unrecognized olecranon or prepatellar trauma. The inciting event may be relatively trivial, such as when a person leans on the elbow or bumps the knee. The same population predisposed to septic bursitis is at risk for the development of traumatic bursitis. Crystal-induced bursitis most often occurs in patients with a history of gout. In one series of 15 patients, approximately 40% of those examined had concurrent acute gouty arthritis

(McAfee JH, Smith DL: Olecranon and prepatellar bursitis—Diagnosis and treatment. West J Med 1988 Nov; 149:607-610)

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at an adjacent or nearby joint. A minor bursal trauma may be a precipitating factor by causing intrabursal crystal shedding. Although seen infrequently, a case of calcium pyrophosphate crystal-induced bursitis from localized chondrocalcinosis may produce similar features. Finally, rheumatoid arthritis may be associated with nonseptic olecranon or prepatellar bursitis. Intrabursal rheumatoid nodules are occasionally present.

Clinical Evaluation

On physical examination, the findings of olecranon and prepatellar bursitis vary, although several features are usually present. Localized bursal swelling over the extensor aspect of the elbow or knee is universally seen. Localized bursal fluctuance is usually present, with bursal fluid volumes ranging from a few drops to 40 ml. An especially important finding is that painless passive range of motion of the knee or elbow joint is preserved except at extreme flexion where the swollen bursal compartment may become compressed. Generalized joint swelling, inflammation, and a restricted range of motion imply that arthritis is present. In most cases, an arthrocentesis should be done.

Septic Bursitis

Septic bursitis involves the olecranon bursa about four times more often than the prepatellar bursa. Bursal tenderness is present in 90% to 100% of patients, and an abrasion or laceration over the bursa is present in about 50% of patients. Most patients with septic olecranon or prepatellar bursitis present with swelling and peribursal cellulitis. Other findings include fever—40% to 90% of cases—or a mild "sympathetic" effusion of the adjacent joint.

Nonseptic Bursitis

A nontender bursal effusion is typical of traumatic and idiopathic bursitis, although as many as 45% of patients may have mild bursal tenderness. About 25% of patients have mild peribursal edema, warmth, and erythema. Fever and other systemic signs of infection do not complicate cases of traumatic and idiopathic bursitis.

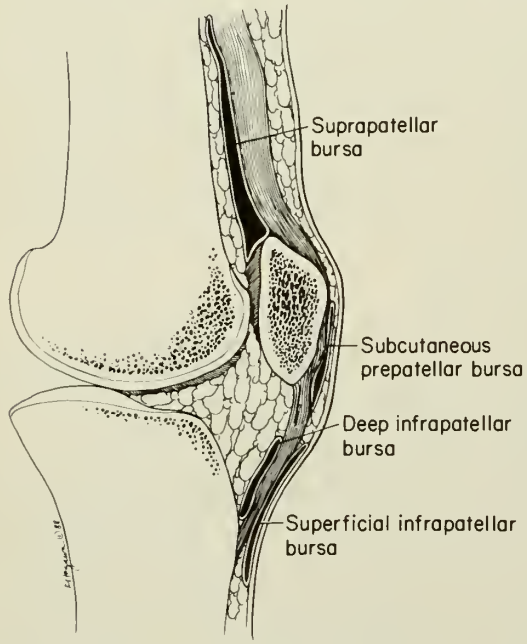

Figure 1.—The drawing shows a lateral view of the bursal anatomy of the anterior knee.

TABLE 1.—*Clinical Features of Septic and Nonseptic Olecranon and Prepatellar Bursitis*

	Forms of Bursitis		
Clinical Feature	*Septic*	*Traumatic and Idiopathic*	*Crystal-Induced*
History of trauma	Common	Common	Occasional
Bursal tenderness	Very common	Occasional	Very common
Skin abrasion or wound	Common	Occasional	Rare
Local warmth	Common	Rare	Common
Local erythema	Common	Rare	Common
Surrounding cellulitis	Common	Occasional	Rare
Fever	Common	Absent	Occasional

The physical findings in patients with crystal-induced bursitis reflect an acute inflammatory process. Canoso and Yood reported 15 cases of acute gouty bursitis. All patients had signs of acute bursal inflammation. Three of the patients had low-grade fever, and six patients had concurrent gouty arthritis.

Characteristics of Bursal Fluid

The medical history and physical examination may not suffice to distinguish septic from nonseptic bursitis (Table 1). An aspirate of fluid from the affected bursa should be examined routinely to establish the cause of the bursitis and to direct therapy. Using aseptic precautions, an 18- or 20-gauge needle is introduced into the bursal cavity from a lateral approach. Aspiration from the extensor side of the knee or elbow should be avoided because of the higher risk of chronic fluid drainage. Unless a history of significant trauma exists, routine knee or elbow radiographs are not necessary.

Septic Bursitis

Bursal fluid is septic when clinically unmistakable pus is aspirated. In a few cases, however, the fluid will be straw colored or serosanguineous. Leukocyte counts of bursal fluid tend to be lower than those for joint synovial fluid. Thus, although the cell count may be more than 200,000 per μl, septic bursitis must be suspected with neutrophil counts as low as 1,500 per μl. The glucose concentration of bursal fluid is often less than 50% of the serum glucose concentration. We routinely measure bursal fluid glucose, although the usefulness of this value for distinguishing septic and nonseptic bursitis is not established. Gram's stains of culture-proven septic bursal fluid are negative in about 30% of cases and cannot be relied on to exclude a diagnosis of septic bursitis.

Aspirated fluid should be cultured routinely. In most aspirates of infected fluids, positive cultures will yield *Staphylococcus aureus* or *Staphylococcus epidermidis* (90%), or streptococcal species (9%). Rarely is septic bursitis caused by anaerobes, mycobacteria, fungi, *Haemophilus influenzae,* or other gram-negative organisms.

Nonseptic Bursitis

Fluid specimen cultures in cases of traumatic and idiopathic bursitis are sterile by definition. The gross appearance of the bursal fluid ranges from straw colored to bloody. The leukocyte count of the fluid is usually less than 1,500 per μl, with mononuclear cells predominating. A leukocyte count in the range of 10,000 to 20,000 per μl is rare. The erythrocyte

TABLE 2.—*Characteristics of Bursal Fluid in Patients With Septic and Nonseptic Olecranon and Prepatellar Bursitis*

Characteristic	Type of Bursitis		
	Septic	Traumatic and Idiopathic	Crystal-Induced
Appearance	Purulent; may be straw colored or serosanguineous	Straw colored, serosanguineous, or bloody	Straw colored to bloody
Leukocytes, per μl	Range, 1,500 to 300,000; mean, 75,000	Range, 50 to 11,000; mean, 1,100	Range, 1,000 to 6,000; mean, 2,900
Differential count	Predominantly polymorphonuclear cells	Predominantly mononuclear cells	Highly variable
Ratio of bursal fluid to serum glucose	<50%	>50%	Unknown
Gram's stain	Positive in 70% of cases	Negative	Negative
Crystals present	No	No	Yes
Culture results	Positive	Negative	Negative

count averages 20,000 to 30,000 per μl. The fluid-to-serum glucose ratio is usually greater than 50%. Bursal fluid typically has a low viscosity, and tests such as the mucin clot or string sign offer no diagnostic information.

Crystal-induced bursitis is most often caused by gout, and negatively birefringent, needle-shaped monosodium urate crystals will be visible by polarized light microscopy. One case of olecranon bursitis caused by deposits of calcium pyrophosphate dihydrate crystals has been reported. The gross appearance of gouty bursal fluid varies greatly, ranging from straw colored to bloody. Cell counts overlap those of bursal fluid in cases of septic and nonseptic bursitis, ranging from 1,000 to 6,000 per μl with a highly variable differential count. Fluid glucose values in cases of gouty bursitis have not been reported. A high index of suspicion for concurrent septic and gouty bursitis should be maintained, as this has been reported.

Table 2 summarizes the typical fluid characteristics in patients with septic, traumatic, and gouty bursitis. We recommend that all olecranon and prepatellar effusions be aspirated at the time of the initial presentation. Fluid analysis should include a cell count with differential, Gram's stain, culture and sensitivity tests, and crystal examination. We also include serum and fluid glucose determinations.

Treatment

The findings of an inflamed olecranon or prepatellar bursa coupled with a positive Gram's stain of bursal fluid require prompt, empiric antibiotic coverage. In addition, empiric therapy for septic bursitis in a case of a negative Gram's stain is warranted when clinical and laboratory features suggest the presence of septic bursitis. Given that septic bursitis is usually caused by *S aureus,* the drug of choice for initial treatment is a penicillinase-resistant penicillin, such as oxacillin sodium, 2 grams taken orally per day. Subsequent therapy can be modified when results of culture and sensitivity tests are known. Patients with mild penicillin allergy—that is, urticarial reactions—can probably be treated with a first-generation cephalosporin such as cephradine, 1 to 2 grams per day, although its efficacy in septic bursitis is unknown. Patients with severe penicillin allergy should be admitted to hospital and treated with intravenous vancomycin hydrochloride, 2 grams per day in divided doses. An alternative outpatient treatment with oral erythromycin, 2 grams per day, can be instituted for mild cases. Treatment failures with erythromycin have been documented, however, and its use requires careful follow-up and repeat bursal aspiration to verify a cure.

Penicillins have been shown to achieve sustained bursal concentrations several times the minimum bactericidal concentration of *S aureus* when administered intravenously or orally. Ho and Su have shown that semisynthetic penicillins—for example, oxacillin or dicloxacillin—were efficacious in treating 25 cases of septic prepatellar and olecranon bursitis. Repeat bursal aspirations were analyzed every one to three days, and antibiotic therapy was continued for five days after the fluid was sterile. It took an average of four days of treatment until the aspirate contained no *S aureus,* though occasionally a duration of as long as two weeks was required. No recurrences were noted on follow-up. This study indicates that a 14-day course of oral antibiotics will cure most cases of septic bursitis. Severe bursal infection, characterized by intense peribursal cellulitis or wound infection, high fever, and systemic toxicity, requires more aggressive inpatient treatment. Under these circumstances, initial treatment with a regimen of intravenous antibiotics followed by a two-week course of oral antibiotics will generally achieve cure.

Several factors may prolong the usual course of septic bursitis. The presence of infection for more than two weeks before antibiotic therapy is begun is associated with persistently positive cultures of serial bursal aspirations. In addition, patients with a history of septic or nonseptic bursitis, rheumatoid nodules, gouty tophi, impaired host immunity, severe bursal infection, or infection with unusual organisms may require an extended course of antibiotic therapy.

In all patients, purulent material should be aspirated at one- to three-day intervals as long as effusion persists. Surgical incision and drainage are rarely necessary and may prolong the overall healing time. Percutaneous suction and continuous irrigation, however, are beneficial in patients with severe septic bursitis when antibiotic therapy and repeated bursal aspiration have not been successful. Additional supportive measures include warm soaks, frequent dressing changes for an associated wound, and protecting the bursa from further trauma. Injecting antibiotics into the bursal space has no documented efficacy for bacterial septic bursitis. In rare cases when infection with *Prototheca* (an algae-like microorganism) induced olecranon bursitis, the intrabursal administration of amphotericin B was effective.

Little information is available regarding the treatment of nonseptic bursitis. Weinstein and colleagues retrospectively reviewed the usefulness of intrabursal steroid injection for traumatic and idiopathic olecranon bursitis: 22 patients who received no therapy beyond an initial bursal aspiration were compared with 25 patients who received a single injection of 20 mg of triamcinolone hexacetonide. In patients treated conservatively, the bursal effusions tended to gradually resolve, with about 70% of all effusions resolved a month after aspiration, and 90% of all effusions resolved after six months. In contrast, there was a prompt response to intra-

bursal steroid injection, with about 85% of effusions resolved after one week. Significant complications were noted in the group given steroids, however. These included skin atrophy over the bursa in 20%, chronic pain associated with pressure applied to the elbow in 30%, and the development of septic bursitis in 10%. Until further data are available, we recommend a conservative approach to treating traumatic and idiopathic bursitis. This includes initial aspiration, applying compressive dressings, such as an Ace bandage, and administering nonsteroidal anti-inflammatory agents for 10 to 14 days. Repeated bursal aspiration is generally of little value. Steroid injection using 10 to 20 mg of a short-acting corticosteroid—such as triamcinolone acetonide—is best reserved for refractory cases. Other unproved but reported therapies for protracted cases include the use of a "blood patch injection" into the bursal compartment, or the temporary (three-day) use of a percutaneous intrabursal drainage catheter.

Crystal-induced bursitis usually responds to treatment with nonsteroidal anti-inflammatory agents or oral colchicine. An intrabursal steroid injection could also be considered, though the potential for complications noted above exists.

Prevention and Complications

Avoiding local trauma is important in preventing and successfully treating both septic and nonseptic bursitis. Persons with prepatellar or olecranon bursitis should be encouraged to avoid leaning on their knees or elbows. When an occupation or avocation places a person at risk for recurrent knee or elbow trauma, protective pads used over the extensor aspect of the knees and elbows may also be beneficial. Recurrent olecranon bursitis may be caused by an underlying olecranon bone spur. Resection of the spur is occasionally necessary.

Most cases of olecranon and prepatellar bursitis resolve without complication. Bacteremia arising from a septic bursitis has rarely been reported. This complication should be considered in immunocompromised patients with septic bursitis who have signs of systemic toxicity such as chills, fever, or hypotension. These patients may be infected with pathogens other than the usual skin flora. In this setting, even with a negative bursal fluid Gram's stain, empiric treatment with broad-spectrum intravenous antibiotics is warranted after the results of blood cultures are obtained. Septic bursitis extends to involve the associated joint or underlying bone in cases of immunocompromised hosts or where antibiotic therapy was delayed.

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Seminars in Health Care Delivery

Whither Malpractice Litigation?

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This feature appears regularly in THE WESTERN JOURNAL OF MEDICINE. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

STEVEN A. SCHROEDER, MD
Series' Editor

Existing tort reform has produced moderating effects on some states, particularly California. Continued escalation of claims frequency, however, and average paid-claim costs mean that other remedies will have to be sought if the professional liability problem is to be solved. Many sources, including the American Medical Association, have proffered radical changes, but most of these changes will cost more than physicians and hospitals can afford. Therefore, the availability of additional funds will determine the next stage of reform. In the meantime, physicians must become more expert in medical staff peer review if they expect to successfully affect future developments.

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The current malpractice litigation crisis involving the cost and availability of liability insurance is gathering steam. In the past two years some physicians have had to pay more than $100,000 for their insurance, while some others found they could not get it at all. Though physicians in California and a few other states benefited from a legislative response to the 1970s crisis, there are still many, including some in Western states, still searching for answers and an escape from the present cycle. Reports from task forces in New Jersey, Florida, and New York have been issued: State of New Jersey, "Task Force on Medical Malpractice," 1987; State of Florida, "Academic Task Force for Review of the Insurance and Tort Systems," 1987; New York Department of Health, "Analysis of Physician Malpractice Claims Closed, 1980-1983," 1987. The United States Department of Health and Human Services has published its report,[1] and the American Medical Association has issued its recommendations.[2]

A lot has been happening in the East, much of which does not seem to be pertinent to the West Coast, but we should not be misled. Tables 1 and 2 summarize a report from the 1987 US General Accounting Office on medical malpractice.[3]

California's increasing rate of claims is in the same ballpark as Florida's between 1980 and 1984 (Table 1), but Florida had a substantial head start in 1980 in average claim costs (Table 2). It may be just a matter of time before the figures for California are as high. Rather than be complacent, therefore, this may be a good time to take inventory of what has happened, what is now being considered, and the best bets for the long term.

California 13 years ago led in tort reform by legislating the following major elements in an attempt to control average claim costs in the area of malpractice litigation:

- Abrogated the collateral source rule that avoids double payment of medical care and disability for patients who incur adverse outcomes from medical management (by 1985, 22 states including 5 of 10 in the West had legislated on this)[4];
- Instituted a $250,000 limit on noneconomic loss (pain and suffering) (by 1985, 15 states including 3 of 10 in the West had legislated on this)[5];
- Approved dividing large-summed verdicts for future medical care into periodic payments instead of requiring a defendant to pay in one lump sum (by 1985, 22 states including 4 of 10 in the West had legislated on this)[6];
- Established limits on contingent fee recoveries of attorneys representing injured patients (by 1985, 30 states, 7 of 10 in the West, had legislated on this).[7]

TABLE 1.—*Frequency of Claims Reported per 100 Physicians**

	1980	*1984*	*% Increase*
Arizona	6.6	8.6	30
California	20.4	26.6	27
Florida	20.8	26.1	25
New York	27.1	35.7	32

*From the US General Accounting Office.[3]

TABLE 2.—*Average Claim Paid for Physicians**

	1980	*1984*	*% Increase*
Arizona	$31,619	$ 51,685	63
California	32,963	61,774	87
Florida	80,556	140,594	75
New York	46,789	104,810	124

*From the US General Accounting Office.[3]

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Danzon for the Rand Corporation[8,9] and Milliman and Robertson for the American Medical Association[10] have shown that these legislative moves will lead to a partial stabilization of insurance payouts. They concluded that there will be a 28% saving in premium costs. More recently Danzon claims that the collateral source offset reduces malpractice awards by as much as 11% to 18%, that limits on liability reduce average claims severity by 23%, and that periodic payments cut average settlements by as much as 25%. Interestingly, she admits that controlling attorneys' fees has had no systematic effect on either the frequency of claims or on the size of awards.[1(pp127-134)] Nevertheless, the other savings are not inconsequential.

It may well be that the moderation of premium requirements in California is the direct result of these legislative efforts. But we are in the throes of rising average paid-claim costs and claims frequency despite these legislative efforts.[3] Few experts think that the tort reforms controlling average claim costs constitute the answer to the malpractice litigation dilemma. They are necessary ingredients, but they will not solve the funding problem that physicians and hospitals are facing in the East and those in the West will soon face.

The recent California negotiations between the medical and legal professions and the insurance industry to declare a truce on tort reform for the next five years is of great consequence ("A Legislative Preview: More of the Same in '88," *LACMA Physician,* December 7, 1987, 117:39). It allows a period of moderation for the development of long-term answers that will be mandatory if physicians and hospitals are to survive.

Feasibility of No-Fault Reform

Twelve years ago I administered the Medical Insurance Feasibility Study for the California Medical Association (CMA) and the California Hospital Association (CHA),[11,12]* from which it has been argued that the number of potentially valid claims far exceeds the actual number filed, perhaps by a factor of ten.[13] It is likely that the majority of patients who do not sue have experienced relatively minor damage—that is, 65% of patients with potential liability cases have only temporary disability or, at worst, slight permanent injury. Most attorneys representing injured patients correctly conclude that processing a malpractice claim is so expensive that an injury suit must have a potential jury award of at least $50,000 to make it worthwhile under the contingency fee system. Therefore, for economic reasons, many legitimate cases fail to become claims. Of the remaining 35% of potential liability cases, those that result in permanent damage or death, less than half ever come to litigation. Thus, a great number of adverse outcomes from medical and surgical management are not pursued, far more than result in claims.

The diagram given in Figure 1 is helpful in establishing a perspective on various options. "A" represents all patients who have suffered some form of adverse outcome from medical, surgical, or hospital management severe enough to require admission to a hospital, extend the stay, or require prolonged outpatient care. "B" represents all the episodes of daily conduct of members of the health care team that could be defined as legal fault. Current monitoring systems are incapable of measuring all of these episodes. Only well-structured and faithfully operated systems at hospital and medical staff levels have the opportunity to come close to measuring the frequency and severity of these episodes. "C" represents the overlap between "A" and "B," comprising the patients who have incurred adverse outcomes because of some form of legal misconduct (fault) of one or more members of the health care team. As I have indicated previously, the 1977 study suggests that fewer than one in ten of patients in the "C" area actually initiates litigation. Presumably patients in the "C" zone should succeed in a lawsuit or claim filed against the offending health care provider. Even so, we are overwhelmed with the cost of this litigation without addressing any of the needs of other patients who may have legitimate claims but never file them.

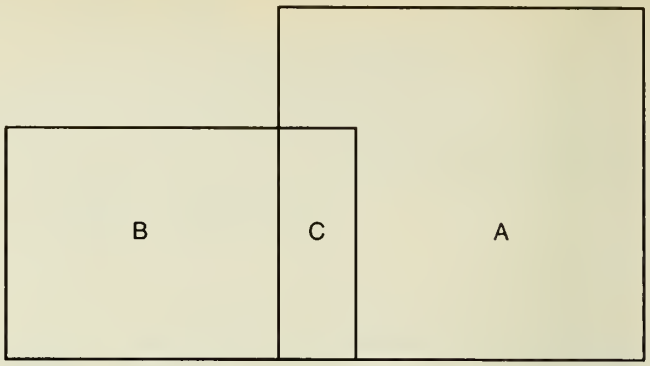

Figure 1.—The diagram illustrates the elements in malpractice litigation. A + C = patients who incur adverse outcomes from health care management, B + C = patients who are subjected to acts of legal misconduct by member(s) of a health care team, C = patients with adverse outcomes due to legal misconduct who should be able to sue successfully.

A broad-based no-fault system would attempt to compensate all patients who have suffered some form of adverse outcome from medical, surgical, or hospital management. This includes everyone in the "A" zone as well as in the overlap "C" zone. Actuaries used the information from the 1977 CMA/CHA study and concluded that even with scheduled benefits of the Workman's Compensation system, the cost of compensating everyone with adverse outcomes would be three to four times more than was then being paid for malpractice insurance premiums. This conclusion was predicated on the assumption that everyone who incurred a measurable adverse outcome would be automatically compensated whether or not a claim was filed.

Such a system was not economically feasible then and may not be today if the source of funds is still limited to members of the health care team. It is conceivable, however, that the entire health and liability insurance industry could establish a complete collateral-source system that would make a no-fault scheme desirable. Remember that most people who suffer adverse outcomes have those outcomes paid for either through health, disability, or other insurance sources or through state or federal medical care plans. There is no reason why these could not be combined with funds from the carriers of malpractice insurance so that the source of funds would be spread among the entire population and not just among members of the health care team.

Other Alternatives

Most of the concerns of more limited compensation schemes are confined to patients in the "C" zone. The American Bar Association's commission on medical malpractice created a "designated compensable event" concept[14] by

*This study is being replicated and expanded in New York under a Robert Wood Johnson Foundation grant to the Harvard University School of Public Health.

which easily identified, fault-based adverse outcomes from surgical and medical procedures would be automatically compensated, leaving the others in the "C" zone to fend for themselves. This excludes the more likely cases that enter litigation today and makes offers of settlement at reasonable costs and with prompt payments. This concept is presently undergoing cost accounting by the Robert Wood Johnson Foundation.

The Moore-Gephardt bills of 1984 and 1985 constitute unique efforts to compensate patients in the "C" zone.[15,16] They allow members of the health care team to examine their own "C" zones to determine who may be likely to bring a lawsuit or file a claim against them. Having made that determination, the physician or hospital can then make an offer that, if reasonable, the patient will accept. This keeps the patient out of litigation with all of its attendant costs. It also allows a patient who files a claim to be the beneficiary of an offer by the defendant that, if reasonable, forecloses continuation in the ordinary course of civil litigation.

Surprisingly, these bills received little medical recognition despite the fact that they would place substantial control of the system in the hands of health care teams. Private concerns were that too many patients in the "C" zone would be compensated, costing more than is presently being paid in malpractice insurance premiums. The other shortcoming of the bills was that a health care provider would have only 180 days in which to make a reasonable offer. This would require a claims handling system that can make proper evaluations day in and day out with greater speed than presently exists anywhere in this country. It is hoped that these bills will be amended to allow a longer period, and, if they are, serious consideration should be given to their implementation. It should be remembered, however, that this is a selective extraction of potential claimants from the "C" zone and not an attempt to compensate all patients in that zone.

The American Medical Association and its specialty societies have recently propounded a plan that is directed toward patients in the "C" zone but, by legislative fiat, forces them into a separate civil litigation scheme that is limited to claims management and hearings at the state medical licensing level.[2] By taking cases out of the ordinary civil litigation process involving the courts or even arbitration, this plan attempts to diminish the administrative costs so that more potential claimants can be paid out of existing funds than are currently being compensated. This scheme is also selective because it does not automatically compensate everyone in the "C" zone. A patient must first file a claim. But the idea is to make equitable and prompt compensation to all those who deserve it, thereby inducing deserving persons to file claims.

Four years ago state legislators in Florida proposed a plan based on hearings that used scheduled benefits much like those of Workman's Compensation, with the expectation that most or all of the people in the "C" zone would be compensated fairly.[17] Proper actuarial examination of the patients in the "C" zone, however, discloses that even with scheduled benefits, the cost to fund such a compensation scheme is at least twice that which is now being paid for malpractice insurance premiums (Florida Senator D. J. Barron and Mr Robert White, Director of Claims, Physicians Protective Trust Fund, oral and written communications, May 1984). The American Medical Association's plan may save administrative costs, but it may also increase the bottom-line dollars required to fund the system. I am also concerned about any system that combines the resolution of malpractice claims with the assessment of discipline in a governmental agency.

One of the unique approaches to selective extraction compensation is that of Virginia's medical malpractice claim compensation fund to pay for infants neurologically impaired from mechanical or hypoxic problems during labor, delivery, or neonatal management.[18] This is an attempt to isolate an extremely high-risk problem to cover the injuries with prompt and reasonable compensation. Without it, many obstetricians in Virginia could not purchase malpractice insurance. The plan, which took effect on January 1, 1988, provides that babies with birth-related neurologic injury will be excluded from the ordinary litigation system and placed in a special program. An infant who qualifies will receive all necessary medical and rehabilitation expenses as they accrue. There will be no payment for pain and suffering, and all collateral sources of revenue will be used. Physicians and hospitals will still be the major sources of the funds for this scheme, but for the first time *all* liability insurance carriers—not just professional liability carriers—will participate. Because this approach places some predictability into the awards for neurologically impaired infants, one carrier agreed to resume covering obstetricians in the state. There is no reason why this concept cannot be used for other high-risk procedures, possibly in the neurosurgical field or other specialties that may be overwhelmed by the spiraling costs of the current litigation arena.

All of the previously mentioned options involve some form of change in the civil litigation system, but each will be successful only if potential claimants are precluded from opting for the civil litigation system. No system will succeed if it does not have exclusivity. Finally, no system should be seriously considered for implementation until it has been subjected to proper actuarial accounting. In this regard, the Moore-Gephardt concept may be the least costly of the lot because it relies merely on private negotiations. The designated compensable event plan is probably even less costly, but it does not include adverse outcomes beyond complications of surgical procedures. That is, adverse outcomes from diagnostic errors or delays in doing procedures would not be included as they would be in the Moore-Gephardt scheme. None of the plans described previously focus on patients outside the "C" zone except a broad-based no-fault compensation scheme.

New Jersey is considering altering the system of malpractice insurance coverage in an effort to ease the current burden on high-risk medical and surgical specialists. The plan is called "channeling," which calls for hospitals to purchase malpractice insurance for themselves and their employees and all members of medical staffs. This will avoid finger pointing between carriers when several defendants are involved, and it will keep down administrative and investigative costs. It will create an inducement for hospitals and their medical staffs to cooperate with respect to injury prevention and credentialing. One major insurance carrier claims that with the channeling concept, a substantial number of physicians will be insured in the next seven years.[19] Physicians will need the protection of strict underwriting and claims allocation guidelines to make sure that their own underwriting records are not adversely affected by administrative management policies. That is, when physicians leave one hospital to go to another hospital to practice, they will take their under-

writing records with them. The question is whether those records will contain allocation of liability in cases where the liability actually rested on other physicians or the hospital rather than on the first physician. Having a single policy cover many defendants makes sense economically, but it will require close monitoring to ensure equity.

The Need for Effective Peer Review

Legislatures have exacted a tacit quid pro quo for instituting our tort reforms by increasing the jurisdiction and clout of state licensing boards. Many legislators seem to think that physicians who commit malpractice are "bad apples" and that the frequency of malpractice litigation can be reduced by taking away or restricting those physicians' licenses. There is no question that there are some bad apples among physicians. One study has shown that as few as 1% of all physicians in Pennsylvania are responsible for 25% of that state's excess carrier losses.[20] Nearly half of the amount of paid claims in Florida was accounted for by physicians with two or more paid claims (State of Florida, "Academic Task Force for Review of the Insurance and Tort Systems," 1987), but all this does is to point to a small group of physicians who warrant closer scrutiny. Certainly bad apples should be identified and either restricted or asked to leave the profession. But even if all are identified, the major source of malpractice litigation is still not addressed. Most lawsuits, even successful ones, are brought against competent, thoughtful, and dedicated physicians who nevertheless occasionally make errors, even negligent ones. Most of the patients in the "C" zone are those of good physicians. Such physicians will never appear before licensing boards unless by some quirk they are targets of a disproportionate number of lawsuits. But even multiple paid claims are not indications of poor quality; they are merely indications that the involved physicians need to be examined more closely. The only study published on this issue is in *Medical Economics* out of Oregon where Dobson found that 100 physicians in that state had 486 claims, but of these 100 physicians, fewer than 10 needed to alter their practice methods and only a handful of these were actually bad apples.[21]

Because most malpractice claims and suits arise from hospital practice involving competent physicians, the only place we can really attack the problem of claims frequency is at the hospital and medical staff level, using quality assurance and risk management programs. Unfortunately, most quality assurance programs, although well intentioned, are abject failures. This must change, for it is only at the hospital and medical staff level that adequate data exist for preventing injuries and correcting practice. It is at this level, not at the licensing level, that we should be focusing. Licensing boards and medical societies do not receive sufficient data to make the kinds of informed decisions that might significantly affect the frequency of adverse outcomes, particularly those with potential liability. Such information is generated only in the areas of hospital care where patterns and problems can be detected. Only at this level can an effective system of peer review be instituted—one that emphasizes respect for prevention rather than a fear of retribution. If physicians realize that participating in quality assurance and peer review programs in hospitals might have a positive impact on malpractice litigation by reducing the number of adverse outcomes, perhaps a breakthrough can be achieved.

Unfortunately, the fear of legal involvement seems to engulf us all. We worry about physicians who lose some or all of their privileges because they seem bent to litigate. According to a Texas survey published last year, 50% of physicians are "somewhat reluctant" and more than 15% are "very reluctant" to review their peers' performances.[22] Taking such a defensive stance is disastrous because it curtails physicians' ability to control the standards of medical practice. Ironically, these same physicians complain that existing peer review systems are not effective. A reluctance to participate in the system and the ineffectiveness of the system may go hand-in-hand.

More than 50% of the surveyed physicians said they would be more likely to participate in the peer review process if they were offered more effective protection against lawsuits from their colleagues. For this reason, the Health Care Quality Improvement Act of 1986 was passed to encourage professional review activities undertaken in good faith.[23] This legislation will be of great benefit for states that do not already have peer review immunities. For states that do have such immunities, this new federal legislation provides an added protection in the form of restricting federal antitrust actions. Unfortunately, the many improvements offered by this new act fail to remedy an intrinsic defect in existing laws. Offended physicians can still take their peer review colleagues and hospitals to court merely by pleading that one or more of the grounds for establishing immunity have been violated. Most suits on those grounds fail. But even with that knowledge, physicians are so tense about the legal system and so concerned about their own economic security that they are reluctant to institute medical staff disciplinary action. A solution to this is to take away aggrieved physicians' ability to sue their reviewers, leaving them with immediate appellate court review of the peer review process. Such a remedy would ensure that unwarranted restrictions in physicians' practices would be minimized, if not eliminated entirely, by a timely reversal of inappropriate peer review actions. The immediacy of the appellate review would tend to cut down the damages by lessening the interruption of physicians' practice.

The need for effective medical and hospital staff monitoring and peer review exists regardless of the changes that may occur in the civil litigation system involving malpractice claims and suits. Danzon thinks that the fault system of professional liability has a built-in deterrence for physicians,[8] but this is not reason enough to keep our present approach. As more states entertain partial no-fault programs, as did Virginia, we will see more emphasis on appropriate and effective peer review for injury avoidance. That is, the more we get away from whatever deterrent effect the litigation process may have, the more we will be required to devote to self-inspection but at a level below the licensing boards. Even the usefulness of the proposed data bank required by the 1986 federal legislation rests on the competency of medical and hospital staff self-examination.

Directional Options

Physicians on the East Coast are finding that it may not be economically feasible much longer to exist in the current fault-related litigation system without the benefit of sources of funding other than the pockets of physicians and hospitals. Despite the moderating effects of tort reform, physicians on the West Coast will ultimately come to the same conclusion. Solutions, if any, will probably come in stages.

First we should try to live within our current monetary means by further streamlining the fault system but without increasing the frequency of claimants. We can do this by reducing the number of potential plaintiffs through the Moore-Gephardt method or any similar private contracting system that decreases the cost of administration and indemnity without inducing more patients to seek compensation. The American Bar Association's designated compensable event plan may fit into this category because its expectation is to pay more conveniently those who would already be expected to sue.

Anytime we try to induce deserving patients to enter a compensation scheme, we have to seek additional sources of revenue. This applies to any plan, such as the American Medical Association's, that attempts to increase the "fairness" of compensation. But if we can find new funding sources, I see no reason to continue to limit compensation under a fault concept. Think of the costs and anguish that will be saved when fault finding for compensation purposes is eliminated. Virginia's initial entry into a partial no-fault system, therefore, becomes important, particularly since that state has induced others to become sources of revenue. Perhaps this will be the beginning of "collateral-sourcing" of all third-party payors and liability carriers into a common system. It should be remembered that most people who incur adverse outcomes from medical management, even without fault, have their medical care paid for by some program. The second stage, therefore, involves searching for outside sources of funding, which will provide presently unattainable options such as no-fault compensation.

Changes in insurance coverage such as channeling are only temporary. Channeling will increase hospitals' burden for awhile, but sooner or later the escalation of claims frequency and average claim cost will scuttle it. Channeling focuses attention on peer review, a necessary ingredient in any option we choose to take. Without convincing legislators that physicians do effective peer review, physicians will have a hard time getting society away from the belief that a fault-based compensation system is the only deterrent available. The third stage, therefore, should have been the first, involving a reexamination of peer review systems at levels substantially below those of the licensing boards.

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Disclosure of Sexual Preference to Physicians by Black Lesbian and Bisexual Women

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Physicians' ability to diagnose and treat health care problems, particularly those with a psychosocial component, is facilitated by accurate information concerning the life-styles of their patients. White lesbians have been shown to be generally reluctant to disclose sexual orientation to their physicians, but little, if anything, is known about black lesbians. Black women, self-identified as bisexuals (N = 65) and lesbians (N = 529), were asked whether they had disclosed their homosexual behavior to their physicians. In the sample, only a third of the women had. Previous sexual experiences, both heterosexual and homosexual, were also queried to illuminate patterns of gynecologic health risk factors. Nearly all of the women reported previous heterosexual experiences.

(Cochran SD, Mays VM: Disclosure of sexual preference to physicians by black lesbian and bisexual women. West J Med 1988 Nov; 149:616-619)

While medicine in recent years has paid increasing attention to the medical concerns of American white gay men,[1] less attention has been focused on the health issues of bisexual and lesbian women.[2] Patterns of health problems in the white lesbian population include rates of sexually transmitted diseases in general,[3] *Chlamydia* and resulting pelvic inflammatory disease,[4] menstrual irregularities,[5] and possibly cervical dysplasia, that are lower than those in white heterosexual women, although the evidence for this for cervical dysplasia is contradictory.[3,4] The existence of specific patterns of vaginitis transmission has been suggested,[2] as well as possibly higher rates of alcoholism[6] and perhaps specific problems such as endometriosis and breast cancer.[3]

Extrapolating these findings to the black lesbian population is problematic. Little is known specifically about the lives of black lesbians (V. M. M., "The Impact of Perceived Discrimination on Black Women's Relationships," unpublished data, October 1985). An early study reports that black lesbians have had more extensive heterosexual experiences than white lesbians.[7] In a second study, black lesbians rated themselves on the Kinsey scale as less exclusively homosexual in their sexual behaviors than their white lesbian counterparts, though they were no more likely to have experienced coitus ever or in the previous year.[8] They also reported higher rates of prior heterosexual marriage and were more likely to have had children. This suggests that black lesbian women may be more heterosexually active both in the past and currently than white lesbians. Heterosexual behaviors may conceivably predispose them to a different pattern of gynecologic problems than those reported by white lesbians.

While the sexual orientation of a patient is not always relevant to adequate health care, women are more likely than men to seek medical care for preventive health purposes, especially for diseases of the genitourinary system, for family planning, and for psychosocial reasons.[9] Knowledge of a woman's psychosocial environment, including her sexual history and current sexual behavior, may aid a physician in considering diagnoses that may not be initially entertained and to discard others that are inappropriate. This is particularly true for sexually transmitted diseases. Yet, studies of predominantly white lesbians and gay men indicate that only somewhere between 18% and 49% disclose their sexual orientation to their physician.[3,10,11]

We examine the disclosure of sexual orientation by black lesbian and bisexual women to their physicians. It has been shown among predominantly white women that bisexual women are less likely to disclose than are lesbians.[10] We were interested in whether or not this would also be the case for black lesbian and bisexual women. In addition, we also sought to document both homosexual and heterosexual experiences of a large sample of black lesbian and bisexual women to begin to clarify possible health risks. Elsewhere it has been suggested that screening for sexually transmitted diseases may not be cost-effective with lesbians.[4,6] To the extent that black lesbians are involved in active heterosexual behaviors, however, this advice would be unwarranted.

Methods

Recruiting Participants

Participants were recruited for a study of black lesbians' relationships in several ways. Several black gay organizations, including the National Coalition of Black Lesbians and Gays and local Los Angeles groups, mailed to their female members copies of our questionnaire to complete and return in prestamped envelopes. A postcard included with the questionnaire but returned by mail separately to preserve the anonymity of respondents gave participants an opportunity to request additional questionnaires for friends. In addition, information about the survey was distributed nationally by flyers to lesbian bars listed in publications of the homosexual

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

community and by press releases to gay newspapers. Possible participants were asked to call a listed telephone number if they desired a copy of the questionnaire. Packets of questionnaires were also mailed to businesses nationally, such as bars and bookstores, that cater to a lesbian clientele. About 2,100 questionnaires were distributed in this manner, and 607 women returned completed questionnaires. Of the responses, 13 were excluded for the following reasons: an absence of lesbian sexual experience (two women), self-identified as heterosexual (three), not of Afro-American ethnic minority background (six), and largely incomplete questionnaires (two).

Participants

Questionnaires were completed by 529 lesbians and 65 bisexual women. All participants were black women who reported at least one previous sexual experience with a woman and who were self-identified as either a lesbian or a bisexual woman.

Demographic characteristics of the sample are shown in Table 1. In general, the two samples were similar. The average participant was in her early 30s, well-educated, and from a middle-class background. About two thirds of both samples had never been married and a third reported having had at least one child. Lesbians were no less likely to have had a child or to have been heterosexually married than bisexual women.

TABLE 1.—*Demographic Characteristics of Participants*

Characteristics	*Lesbians, N=529*	*Bisexual Women, N=65*
Mean age, years	33.5±7.7*	31.7±7.8*
Mean socioeconomic background†	3.0±0.8	3.1±0.8
Mean years of schooling completed	15.4±2.6	15.2 ±2.6
Annual income, %		
Less than $5,000	8	11
$ 5,000 to $10,999	17	20
$11,000 to $19,999	35	31
$20,000 or more	40	38
Marital status, %		
Never married	67	61
Formerly married	31	34
Currently married	2	5
Percentage with children	34	39
Geographic region, %		
West, Northwest, or Southwest	50	50
Northeast or East	22	27
Midwest	14	9
South or Southeast	14	14

*± standard deviation. Lesbian and bisexual participants do not differ significantly.
†A score of 3.0 is equivalent to a middle-class background.

TABLE 2.—*Disclosure of Sexual Preferences to Physician*

Disclosure Answers	*Lesbians, N=529*	*Bisexual Women, N=65*
Does not have a personal physician, %	16	13
Has a personal physician, %	84	87
For those with personal physician		
Physician does not know, %	45	66
Physician may suspect, %	11	7
Physician knows but topic not actually discussed, %	11	9
Physician knows and topic has been discussed, %	33	18

*$P < .05$.

Questionnaire

The 27-page questionnaire covered several topics relevant to women's relationships with love partners, friends, family, and the larger social world. These included disclosure of sexual orientation and previous sexual experiences with both men and women, among other topics. Questions were adapted from an earlier study by one of us (V.M.M.) of black lesbians and studies of white lesbians,[13,14] white gay men,[15] and white heterosexual college students.[16] The questionnaire took about an hour to complete and was self-administered.

Results

Disclosure of Sexual Orientation

Lesbians and bisexuals did not differ in reporting having a personal physician; more than 80% in both groups did. Among those with physicians, however, many assumed that their physicians did not know the participant's sexual orientation (Table 2). For lesbians, about a third (N = 142) had openly talked about their orientation status with their physicians. Another 11% (46) assumed that their physicians knew but said they had not discussed the topic. Bisexual women were significantly less likely than lesbians to have disclosed their same-sex sexual behavior to their physicians (χ^2 [3] = 8.59, $P < .05$). About 18% (10) had talked with their physicians, while another 10% (5) assumed that their physicians knew.

Sexual Experiences

There was a trend for lesbians to report a higher median number of female sexual partners by history than there was for bisexual women (Mann-Whitney $U = 14{,}035$, $P < .06$; Table 3). In addition, lesbians were less likely than bisexual women to report having had heterosexual coitus (χ^2 [1] = 4.36, $P < .05$), though both samples generally reported that they had. As might be expected, bisexual women reported having had significantly more male sexual partners (Mann-Whitney $U = 9{,}961$, $P < .001$) and more recent hetero-

TABLE 3.—*Patterns of Sexual Experiences*

Sexual Experience	*Lesbians, N=529*	*Bisexual Women, N=65*
Female sexual partners, median No.	9	7
Heterosexual experiences		
Has had sexual intercourse, %	90	99*
Male sexual partners, median No.	5	8†
Last previous heterosexual experience, median mo	67	7†
Had coitus in previous year, %	12	65†
Currently heterosexually active, %		
Never	88	44
Rarely	10	36
Sometimes	2	12
Regularly	1	8

*$P < .05$.
†$P < .001$.

sexual involvement both in months since last heterosexual activity (Mann-Whitney $U = 4{,}275$, $P < .001$) and within the previous 12 months (χ^2 [1] = 83.0, $P < .001$). Also, bisexual women reported a higher current rate of heterosexual involvement, with 56% (36) reporting that they were heterosexually active at least "rarely" (χ^2 [3] = 90.1, $P < .001$).

Sexual orientation labels, however, are not always illuminating. As can be seen, within the lesbian sample, 13% of women (63) reported that they were currently heterosexually active at least "rarely" and 12% (58) reported having had coitus within the previous year. Among bisexual women, 44% (28) reported that they were "never" sexually active with men and 35% (22) indicated no coitus in the previous year.

Discussion

With the increasing concern about sexually transmitted diseases, it becomes even more important to understand individual patterns of sexual behavior. This is facilitated by both a knowledge of what is normative for similar persons and frank disclosure by patients. The present study provides important information about the behavior of black lesbian and bisexual women. As with earlier studies of black lesbians,[7,8] respondents in this survey showed extensive previous heterosexual experience. Nearly 90% of the lesbians (472) and virtually all of the bisexuals (64) had had heterosexual coitus. This is similar to the 88% rate reported by Bell and Weinberg for black lesbians in their study.[8] In contrast, research has shown that 80% to 83% of white lesbians have had heterosexual coitus.[7,8,13] While the black lesbians in the present study were less likely to be heterosexually active in the previous 12 months (12%) than black lesbians in the Bell and Weinberg study (33%), our participants were somewhat older and so may have been experimenting less with their sexual behavior in general.

The overall consistency of these findings suggests that black lesbians may, in fact, as a group have more extensive heterosexual experience than white lesbians, although such a conclusion should be viewed as tentative because a direct comparison of similar samples is unavailable. The prevalence of previous heterosexual experience among black lesbians suggests that diagnostic considerations relevant to sexually transmitted diseases, such as *Chlamydia*, should be entertained when treating black lesbian patients. Also, although lesbians are presently at extremely low risk for infection with the human immunodeficiency virus (HIV) responsible for the acquired immunodeficiency syndrome (AIDS),[17] given the higher prevalence rate of AIDS within the black community in general[18] and the possibility that when lesbians are heterosexually active it occurs more often with gay and bisexual men,[19] there may be a need for preventive health education efforts specifically targeted at black lesbians who are or have recently been heterosexually active.

Results reported here provide further evidence that lesbians and bisexual women are often reluctant to disclose their sexual orientation to personal physicians. In an earlier study of primarily white respondents, about 47% of lesbians and 30% of bisexuals had told a gynecologist of their sexual orientation.[10] In the current survey of black women, 33% of lesbians and 18% of bisexuals reported having discussed the topic with a physician. If we include the women who believed that their physicians knew of their sexual orientation but who had not actually discussed the matter, then 44% and 27% of black lesbians and bisexuals, respectively, believed that their physicians knew the respondents' sexual orientation. As shown in the earlier study, bisexual women were significantly less likely to disclose to physicians than were lesbians.[10] It seems that black lesbian and bisexual women share the reluctance seen among white lesbian and bisexual women to disclose their sexual orientation to physicians, although the precise reasons for this were beyond the scope of the present study. For black lesbians, problems with disclosure may be twofold. If they do not inform their physicians about their sexual orientation, they are likely, as with white lesbians, to experience health care that is alienating, if not inappropriate.[3,12] If they do disclose and physicians assume a pattern of health risk consistent with white lesbians, they may also receive inadequate care because physicians fail to distinguish differences in life-styles within the lesbian community.[1]

Several methodologic concerns should be kept in mind. First, the women who participated in this study may not be a representative sample of black lesbians and bisexuals. Representative sampling from a hidden population is not possible.[20] Thus, the study may overestimate the prevalence of openness about sexual preference with physicians because the women who returned the survey are more likely to be open about their sexual preference in general. Furthermore, our sample consisted predominantly of urban, educated, and upwardly mobile middle-class black lesbian and bisexual women who were predominantly from the West Coast. Their experiences with the health care system probably differ significantly from those of less educated, lower income black women who are restricted to the use of public health care facilities. This latter group may be less likely to have access to a regular physician with whom they feel comfortable disclosing their sexual preference. Further research is needed that surveys this segment of the black lesbian population.

Nevertheless, results indicate that physicians should not assume that all black women are sexually active only with male partners. As shown here, most black lesbian and bisexual women do not actually discuss their sexual orientation with physicians. A history of childbearing or a previous marriage is not always an indicator of current heterosexual status. Nearly a third of the lesbians in this study had given birth and a similar percentage either had been or were currently married. Nor should physicians assume that the disclosure of a lesbian orientation implies a lack of extensive previous heterosexual experience or current heterosexual involvement that may predispose to particular gynecologic problems, sexually transmitted disease, or HIV seropositivity resulting from heterosexual activity. Kinsey's data clearly show that sexual object choice may not always be an either/or preference.[21] In our overall sample of 594 black women, 91% had had heterosexual experiences, and, for many women, these experiences were extensive. Only the taking of comprehensive sexual histories can avoid problems of assuming exclusive heterosexual or homosexual involvement.

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Clinical Response to Inhaled Steroids

THE BIG ADVANCE, and I think our knowledge is still advancing a lot in how to use these preparations, has been in the development of topical preparations not associated with the systemic side effects of prednisone therapy. These are topical preparations that, when inhaled into the airways, are poorly absorbed, and what is absorbed is so rapidly metabolized that it has little effect on the adrenal pituitary axis. These do not cause the osteoporosis, particularly in postmenopausal women, or the premature cataracts—seen with much greater frequency than has been appreciated—that are associated with oral prednisone therapy for obstructive lung disease.

Davies studied 33 subjects treated with beclomethasone dipropionate (Vanceril) and found decreased daytime and nocturnal symptoms of asthma, decreased need for β-adrenergic aerosols and for prednisone, and an increased measure of forced expiratory flow. And here is the interesting phenomenon: for up to nine months, patients who were requiring prednisone were able to come off it.

Now we have been taught, I think by the pharmaceutical companies themselves, that one month is the therapeutic trial period for an inhaled steroid. I am going to differ with that. If a patient responds to oral prednisone, that patient merits an aggressive trial with an inhaled steroid, and at the end of four weeks, that patient has probably not achieved the maximum benefit that can be obtained from that drug. Some clinical response should be noted, but the maximum effect may not be seen for nine months. In other words, patients with mild, moderate, or even severe asthma, who may be discouraged about their condition after a month on an inhaled steroid, may still improve, and their prednisone requirements will be reduced over the next eight months—a reason for optimism.

—HOMER A. BOUSHEY, MD

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Public Health and Preventive Medicine

Anti-HIV Seroprevalence in California Blood and Plasma Donors

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This is one of a series of articles from the western state public health departments.

California was the first state in the United States to mandate the testing of all donated blood and blood products for evidence of infection with the human immunodeficiency virus (HIV). Regulations requiring HIV antibody screening were promulgated within days after the Food and Drug Administration (FDA) approved the HIV antibody test in 1985. HIV seroprevalence among California blood and plasma donors was recently reviewed and is reported here.

Materials and Methods

Except for specifically exempted donations such as autologous donations, California blood banks and plasma centers are required to test all blood and blood products for HIV antibodies and to discard all units in which the blood is repeatedly reactive on enzyme-linked immunosorbent assay (EIA) testing.[1] Additional confirmatory testing with immunoblot or immunofluorescence assay is not required by law but is recommended by the California State Department of Health Services. Reporting of seroprevalence statistical data on a quarterly basis to the Department of Health Services is also required.[2]

Aggregate serologic test results for all donations were compiled from statistical reports for the fourth quarter of 1987, the most current data available. These data were analyzed and form the basis of this report.

Results

Statistical summaries were received from 55 blood banks and 31 plasma centers. These facilities reported the results of HIV antibody testing for 470,143 units of blood and blood products collected during October through December 1987. This represents data from more than 97% of the facilities required to report and for more than 98% of the blood and blood products collected during this period. The remainder of the reports were incomplete at the time of this communication.

Of the reporting blood banks, 36 (65%) use the EIA test kit produced by Abbott Laboratories and 24 (77%) of the reporting plasma centers use the EIA test kit manufactured by Electro-Nucleonics (Table 1). Among the 55 blood banks and 1 plasma center conducting confirmatory testing, 53 use Western blot, 1 uses indirect fluorescence antibody (IFA) testing only, and two use a combination of Western blot and IFA.

Of the 470,143 units of blood and plasma tested, 647 (0.14%) units were repeatedly reactive for HIV antibodies on EIA testing (Table 2). The repeat EIA seroprevalence was 0.15% at blood banks and 0.11% at plasma centers.

Of the 465 repeat EIA anti-HIV seropositive units identified by blood banks, 44 (9.46%) were confirmed positive with Western blot or IFA (Table 3). This represents a sero-

TABLE 1.—*Enzyme-Linked Immunosorbent Assay Test Kits Selected Among Blood Banks and Plasma Centers*

	Blood Banks			Plasma Centers			
Test Kit Manufacturer	*In House*	*Outside Laboratory*	*Subtotal*	*In House*	*Outside Laboratory*	*Subtotal*	*Total*
Abbott	30	6	36	1	5	6	42
Electro-Nucleonics Inc	0	1	1	4	20	24	25
Genetic Systems	5	4	9	0	0	0	9
Organon	5	1	6	0	0	0	6
Dupont	2	1	3	0	0	0	3
Ortho	0	0	0	1	0	1	1
Total	42	13	55	6	25	31	86

(Perkins CI, Kizer KW, Hughes MJ, et al: Anti-HIV seroprevalence in California blood and plasma donors. West J Med 1988 Nov; 149:620-622)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
EIA = enzyme-linked immunosorbent assay
FDA = Food and Drug Administration
HIV = human immunodeficiency virus
IFA = indirect fluorescence antibody [test]

prevalence of 0.015%, or 1 confirmed positive unit per 6,670 units collected. The only plasma center doing confirmatory testing found no reactive blood among the 1,878 units tested. Including testing results from this facility does not change the overall confirmed seroprevalence.

When examined by the location of the reporting blood bank, the rate of confirmed positive units for anti-HIV was 26 per 100,000 units of blood reported by the blood bank located in San Francisco, 22 per 100,000 units reported by blood banks located in Los Angeles County, and 21 per 100,000 units reported by the blood banks located in San Diego and Orange counties combined (Table 3). Confirmed seroprevalence rates were 13 per 100,000 units at blood banks located in the San Francisco Bay Area counties other than San Francisco and 2 per 100,000 units elsewhere in the state. In comparing these rates, it should be remembered that many blood banks have several donation facilities and often report for counties other than the one in which they are located. In practice, this may result in higher prevalence areas—such as San Francisco—having lower rates than if they collected only within the area they serve.

Units of blood collected at blood banks located in San Francisco and Los Angeles counties were 2.72 times more likely to be confirmed positive than those collected elsewhere in the state (95% confidence interval, 1.48 to 5.00). This is consistent with the greater per capita cumulative incidence of the acquired immunodeficiency syndrome (AIDS) in these areas (Table 3).

Of those facilities doing confirmatory testing, 35 blood banks and 1 plasma center reported gender-specific data.

TABLE 2.—*Results of HIV Antibody Testing With the Enzyme-Linked Immunosorbent Assay (EIA)*

Facility Type	No. of Facilities	Total Units Tested	Repeatedly EIA Reactive No.	Repeatedly EIA Reactive %
Blood bank	55	300,852	465	0.15
Plasma center	31	169,291	182	0.11
Total	86	470,143	647	0.14

HIV = human immunodeficiency virus

Collectively, these facilities tested 99,002 units of blood. In all, 12 (0.022%) units donated by men and 1 (0.002%) of the units donated by women were confirmed positive for HIV antibodies (Table 4). The blood donated by men was 9.5 times more likely to be confirmed HIV-positive than that donated by women (95% confidence interval, 1.79 to 50.11). The confirmed seroprevalence rate at facilities not reporting gender-specific data was 0.015%, which was not significantly different from the confirmed seroprevalence among facilities where data by gender were available.

Assuming that the number of confirmed positive units of blood represents the true seroprevalence of anti-HIV for this selected population of blood donors, the positive-predictive value of repeat EIA screening at facilities reporting gender-specific data was 6.84%. That is, the probability that a repeatedly EIA-reactive specimen would be confirmed positive was 6.84%. The positive-predictive value was 10.4% among blood donated by men and 1.3% among blood donated by women. These predictive values are consistent with the overall low HIV seroprevalence in California blood and plasma donors and the high sensitivity and specificity of the EIA test kit.[3] The higher prevalence of false-positives among women has been reported previously and is primarily due to host antibodies reacting with human leukocyte antigens on the lymphocyte line used to culture the AIDS retrovirus.[4-8]

Comment

Seven EIA test kits are currently licensed by the FDA. Clinical studies by test kit manufacturers indicate that the sensitivity and specificity of all test kits are greater than 99%.[9] All reporting facilities are using FDA-licensed EIA test kits. The actual sensitivity and specificity in routine use depend on the quality of testing in the laboratory, the test kit used, and the frequency of the HIV antibody in the population studied. Because of the lack of confirmatory test data from plasma centers, the significance of results based on different test kits selected between blood banks and plasma centers cannot be evaluated with these data. The lower prevalence of repeat EIA-reactive units at plasma centers may reflect the practice of frequent repeated donations by seronegative persons (plasma donors may donate as frequently as every 48 hours, while blood donors must wait eight weeks between donations).

Statewide HIV-antibody testing data for blood banks were not systematically analyzed before July 1987, although selected information was routinely ascertained. Results from the fourth quarter of 1987 are virtually unchanged from

TABLE 3.—*Results of HIV Antibody Testing in California Blood Banks for the Fourth Quarter of 1987**

Location	Number of Blood Banks	Number of Units Tested	Initially EIA Reactive No.	Initially EIA Reactive % Tested	Repeatedly EIA Reactive No.	Repeatedly EIA Reactive % Tested	Confirmatory Reactive No.	Confirmatory Reactive % Tested	Confirmatory Reactive % EIA++	Cumulative AIDS Incidence/10,000 Population†
San Francisco	1	23,023	65	0.28	19	0.08	6	0.026	31.58	53.4
Los Angeles County	29	109,516	483	0.44	106	0.10	24	0.022	22.64	5.7
Orange and San Diego counties	5	24,317	134	0.55	94	0.39	5	0.021	5.32	2.9
Bay Area, not San Francisco‡	6	54,537	416	0.76	124	0.23	7	0.013	5.65	3.3
Other§	14	89,459	345	0.39	122	0.14	2	0.002	1.64	1.3
Total	55	300,852	1,443	0.49	465	0.15	44	0.015	9.46	

AIDS = acquired immunodeficiency syndrome, EIA = enzyme-linked immunosorbent assay, HIV = human immunodeficiency virus, ++ = repeatedly positive

*Blood banks may collect from individuals or report for facilities located in other counties.
†Based on AIDS Case Register, California State Office of AIDS, May 9, 1988.
‡Alameda, Contra Costa, San Mateo, Santa Clara, Solano, and Sonoma counties.
§Butte, Fresno, Humboldt, Imperial, Kern, Merced, Monterey, Riverside, Sacramento, San Bernardino, San Joaquin, San Luis Obispo, Santa Barbara, Shasta, and Ventura counties.

TABLE 4.—*Human Immunodeficiency Virus Antibody Testing According to Donor Gender in 35 California Blood Banks and 1 Plasma Center*

Donor Gender	Number of Units Tested	Initially EIA Reactive		Repeatedly EIA Reactive		Confirmatory Positive		
		No.	% Tested	No.	% Tested	No.	% Tested	% EIA++
Male	55,339	331	0.60	113	0.20	12	0.022	10.62
Female	43,663	214	0.49	77	0.18	1	0.002	1.30
Total	99,002	545	0.55	190	0.19	13	0.013	6.84

EIA=enzyme-linked immunosorbent assay, ++=repeatedly positive

those of the third quarter of 1987, which have not been published.

Interviews conducted of a sample of seropositive blood donors in California identified since testing began indicate that most donors with HIV antibodies are men who had sex with other men but who did not perceive themselves as gay or bisexual (P.V.H., unpublished data, May 1988). These findings are consistent with the dominance of male seropositives in this study and may partially explain the higher seroprevalence among blood donors in areas with a high AIDS incidence. These concordant data support the assessment that, at present, HIV infection is not widespread outside of recognized AIDS-risk groups in California.

On comparing the current data with prior blood donor testing results and published reports, it is clear that the proportion of donors confirmed as HIV-seropositive in California in the latter part of 1987 was significantly lower than the proportion of persons found HIV-seropositive in California and elsewhere during 1985. For example, in 1985, the American Red Cross reported that 110 of 100,000 units of blood collected in Los Angeles were confirmed positive by Western blot compared with 22 per 100,000 units confirmed positive for the same area in this study.[10] Similarly, in San Francisco in 1985, 150 of 100,000 units were confirmed HIV antibody-positive, while in this study 26 per 100,000 units from that area were confirmed positive.[11] Nationally, the overall confirmed seroprevalence rate among first-time donors has remained stable at approximately 40 per 100,000, but among all donors the confirmed seroprevalence rate decreased from 38 per 100,000 in 1985 to 10 per 100,000 in 1987 (R. Dodd, American Red Cross, Washington, DC, oral communication, January 1988).[12] With the rate in the fourth quarter being 15 per 100,000 in California, the temporal decrease in seroprevalence among blood donors in this state suggests that the widespread availability of state-supported, anonymous antibody testing at California's alternative test sites since the summer of 1985 has been successful in decreasing blood donations by HIV-infected persons. The measures that have been adopted to protect the blood supply from infection due to HIV have apparently been effective.

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Medical Practice Opinion

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Commission on Quality Care Review of the California Medical Association. The opinions offered are based on training, experience, and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions, or policy statements.*

Health Supervision of Children

QUESTION:

What services are considered basic to a general physical examination of an asymptomatic pediatric patient?

OPINION:

It is the opinion of the Scientific Advisory Panels on General and Family Practice and Pediatrics that screening in pediatric practice implies a broad concept that includes comprehensive monitoring of normal growth and development from birth through adolescence. To insure optimal physical and emotional health during critical periods of childhood, health supervision at regular predetermined intervals should be organized around specific issues that may affect either health or the development of a disease. These visits should be part of a comprehensive health system for each child, rather than fragmented, disease-specific screening programs. Continuing contact with the child and family provides an opportunity not only for periodic screening but also for effective evaluation of the child during times of illness.

Primary and secondary screening in office practice should not be limited to searches for physical dysfunction alone. The assessment of the child's social and emotional adaptation in the family, school, and community broadens and enriches the data base on which primary care physicians can direct screening procedures. These recommendations are based on the concept of anticipatory guidance—early recognition of physical, developmental, and behavioral components of a child's life will result in early intervention and appropriate counseling.

Comprehensive office-based examinations for children and adolescents should generally include the following:

- *Physical growth*—linear growth and weight (at each health supervision visit) and head circumference (through the first year). Measurements should be plotted on standardized growth charts.

- *Physical examinations*—Complete physical assessments should vary with age as development alters the potential for abnormal findings—for example, determining hip stability at birth through one year; blood pressure at 3, 5, 8, 12, and 15 years; scoliosis screening beginning at 8 years, and so forth. Vision and auditory/language functions can be assessed beginning at birth. Standardized objective screening tests for vision and hearing should be done when a child is 4 or 5 years old.

- *Developmental assessment*—Motor, social-adaptive, and language function should be monitored objectively. The Denver Developmental Screening Test is one useful, replicable, and valid screening test that may be used from birth through five years; it may complement the history and complete physical examination. Children with chronic diseases and developmental disabilities will need a focused assessment of their developmental functioning in school, home, and the community.

- *Family function*—with an emphasis on parent and child interactions, both discussed and observed.

- *Nutritional assessment*—including a dietary history that emphasizes quantity and quality of food intake—for example, fluoride, iron, proteins, unsaturated fats, unrefined sugar, and fiber intake.

- *Educational assessment*—preschool and day-care experience, kindergarten entry readiness, and response to structured learning.

- *Behavior assessment*—emphasis on individual temperaments and family styles coupled with age-specific knowledge of expected behavioral patterns.

- *Socioeconomic assessment*—emphasis on needs for available assistance with nutrition, housing, and early education of children.

Screening procedures will vary somewhat with regional variables—for example, nutrition (fluoride in water supply), infection (tuberculosis skin test), ethnicity (sickle-cell hemoglobinopathy and screening for Tay-Sachs disease), and social settings (nutritional assistance). Additionally, specific screening procedures, such as hematocrit, tuberculosis skin tests, rubella titer, advice about car seats, swimming safety, and sunscreen protection, will vary considerably with the age of the child. In particular, screening in the adolescent patient may require a focused history on the teenager's understanding of sexuality, substance abuse, risk-taking behaviors, and accelerated change in psychosocial development.

Recommended schedules for health promotion screening in office practice are available in several formats. Persons seeking further information on health supervision of children should consult these references: (1) Standards for Child Health Care and (2) Guidelines for Health Supervision, American Academy of Pediatrics, 141 Northwest Point Boulevard, PO Box 927, Elk Grove Village, IL 60007; and (3) Encounters with Children: Pediatric Behavior and Development, Dixon, SD, and Stein, MT. Year Book Medical Publishers, Chicago, 1987.

Approved: April 1988

This opinion has been prepared by the CMA Scientific Advisory Panels on General and Family Practice and Pediatrics based on available information. It is only an advisory opinion and should not be construed as binding on any individual or as expressing an absolute standard of medical practice. Medical opinion may vary regarding the appropriateness of a particular treatment or service in a given situation. Differences in an individual case should be reviewed by physician medical advisors. Differences of opinion between a medical advisor and attending physician should be referred to the county medical society where the physician practices.

Book Reviews

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

ELECTRODIAGNOSIS IN CLINICAL NEUROLOGY—Second Edition— Edited by Michael J. Aminoff, MD, Professor of Neurology, University of California, San Francisco, School of Medicine; Director, Clinical Neurophysiology Laboratories; and Attending Physician, University of California Medical Center, San Francisco. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 736 pages, $79.

The stated aim of this book is to provide a comprehensive account of the role of electrodiagnostic procedures in clinical neurology. It details the clinical relevance of available procedures to clinical neurophysiology.

To assay the monograph, I read sections pertinent to patients as they presented in a general neurologic practice. As a result, some chapters (Quantitative Electroencephalogram [EEG], Depth Electrography and Electrocorticography, Electroretinography, and Intraoperative Monitoring) were less relevant because of this selection. The material on the electromyogram (EMG), evoked potentials, brain death, EEG, sleep disorders, and pediatric EEG was excellent.

I was pleased with the even presentation of the material. The assessment of old and new tests was not biased. The appropriate use and indications for studies were stressed. References were well chosen and recent.

In short, this is a useful, current monograph for the clinical neurophysiologist. It is recommended for any clinical neurologist engaged in such diagnostic procedures.

DON F. SEELINGER, MD
Clinical Associate Professor of Neurology
University of New Mexico School of Medicine
Albuquerque

* * *

DISEASES OF THE KIDNEY—Fourth Edition—3 volumes— Edited by Robert W. Schrier, MD, Professor and Chairman, Department of Medicine, and Head, Division of Renal Diseases, University of Colorado School of Medicine, Denver, and Carl W. Gottschalk, MD, Career Investigator, American Heart Association, and Kenan Professor of Medicine and Physiology, University of North Carolina School of Medicine, Chapel Hill. Little, Brown and Company, 34 Beacon St, Boston, MA 02108, 1987. 3,506 pages, $195.

The title of this venerable text has been changed in the fourth edition from *Strauss and Welt's Diseases of the Kidney* to *Diseases of the Kidney.* The current editors do not state the reason for this change. I hope future editions will again carry the longer title, which gives the names of Strauss and Welt their well-deserved recognition. Their energies and high academic standards greatly facilitated nephrology's emergence as a strong academic and clinical discipline.

The stated purpose of this three-volume text is "to present in a most authoritative and integrated manner possible, sixteen major areas of diseases of the kidney and urinary tract, with appropriate attention devoted to basic and clinical science." Thus, this text's position in the spectrum of nephrology is different from the other two encyclopedic texts in the field. Brenner and Rector's *The Kidney,* 3rd edition (WB Saunders, 1986), deals with a similar domain, including all of renal physiology, pathophysiology, and clinical nephrology, but places clear emphasis on physiology and related pathophysiology in a rigorous and authoritative two-volume text. Seldin and Giebisch's *The Kidney: Physiology and Pathophysiology* (Raven Press, 1985) contains an extensive but concise and lucid overview of physiology and pathophysiology, with more emphasis even than the Brenner and Rector text on normal physiology. Thus, *Diseases of the Kidney* is at the more clinical end of the spectrum of these three premier texts.

Specific comparisons among the texts are difficult because all three are well-written and cover a huge range of nephrologic material. The reader would not be mistaken to purchase any of the books, and most academic nephrologists would probably purchase or have immediate access to all three. For the clinical nephrology trainee, clinical nephrologist, or internist with a serious nephrologic interest, however, *Diseases of the Kidney* is indispensable.

The organization of the fourth edition is a division into 16 sections. The first section contains nine chapters concerning basic structure-function relationships and basic renal physiology. These chapters provide the foundation for the remaining 15 parts, which cover specific clinical areas of nephrology. The importance of basic science in each of these sections is emphasized by initial chapters dealing with pathophysiology and molecular mechanisms, wherever possible.

The chapters in the basic science section (section 1) are generally of high quality. Those on structure-function relationships, regulation of water balance, potassium, and renal metabolism are particularly strong. Section 2 contains six chapters that cover clinical methods and techniques for evaluation of the kidney, running the spectrum from urinalysis to renal biopsy. The chapter on urinalysis and the chapter on laboratory evaluation of renal function are superior contributions. The one on laboratory evaluation of renal function combines a lucid physiologic approach with specific and critical discussions of the pitfalls of interpreting clinical data on urinary dilution and concentration, plasma electrolytes, glomerular filtration, and renal handling of a wide variety of solutes. An entire section is devoted to hereditary diseases of the kidney, an appropriate emphasis considering the high frequency of these diseases in producing end-stage renal disease, as well as recent advances in diagnostic techniques. The section on urologic diseases is comprehensive and authoritative. It also contains an excellent chapter on urolithiasis, which details an extensive elucidation of pathophysiology.

The section on infections of the urinary tract and kidney is extensive and includes a superior contribution on the topic of host defense mechanisms in urinary tract infections. The more traditional sections on clinical nephrology cover nephrotoxin-induced disease, acute renal failure, hypertension, chronic glomerulonephritis and chronic interstitial nephritis, collagen vascular/hematologic/vasculitis, the kidney in systemic disease, clinical disorders of fluid, electrolyte, and acid base homeostasis, the uremic syndrome, and management of end-stage renal failure. Each of these sections is comprehensive and contains well-written chapters. The final section on nutrition and drugs includes an excellent survey of phosphate and aluminum toxicity.

At 3,500 pages, 3 volumes, the fourth edition more than doubles the length of the second edition published in 1971. It is clear from the scope and quality of this text that the field has attracted terrific scholarship and made great strides in the understanding of the physiology and pathophysiology of this organ as well as in the treatment of renal diseases. It would surprise me very much if there were enough card-carrying nephrologists when the first edition was published in 1963 to have even filled the author list of the current version of this great text. It is also clear from viewing the development of this text, however, that nephrology has matured even more dramatically in its scientific rigor and sophistication than in mere numbers of participants.

HENRY N. HULTER, MD
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Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

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(Continued on Page 631)

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This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director,
Special Programme on AIDS
World Health Organization,
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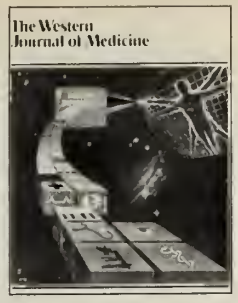

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I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

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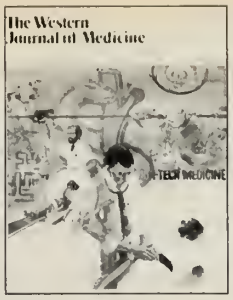

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—R. Paul Robertson, MD

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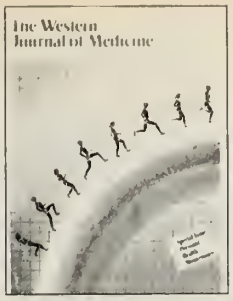

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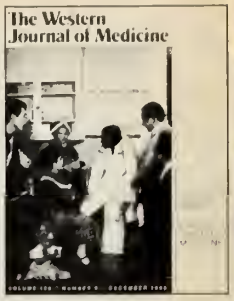

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—Malcolm S.M. Watts, MD

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(Continued on Page 631)

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WARNINGS

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PRECAUTIONS

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Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

Rx
Cardizem®
(diltiazem HCl)
☐ 60 mg ☐ 90 mg
☐ 120 mg
Sig: tid

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope
Nervous System:	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGDT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria
Other:	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing.

References: 1. Schroeder JS: Mod Med 1982;50(Sept):94-116. **2.** Cahn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **3.** O'Rourke RA: Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frahlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlap S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W: Consultant 1984;24(Dec):150-159. **7.** O'Hara MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982;49:560-566. **9.** Feldman RL, Pepine CJ, Whiffle J, et al: Am J Cardiol 1982;49:554-559.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 626)

February 9-10—**Legal Aspects of Occupational Safety and Health.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

February 10-11, May 19-20, August 24-25—**MKSP Review Course, Parts 1, 2, 3.** Seattle. Fri-Sat. May: Fri-Sat. Aug: Thurs-Fri. Contact: VMMC.

February 27-March 1—**Current Issues in Infectious Disease.** Seattle. Mon-Wed. Contact: (206) 326-7349.

March 3—**Neurologic Complications of Systemic Disease.** Seattle. Fri. Contact: VMMC.

March 10—**Management of Problem Wounds.** Seattle. Fri. Contact: VMMC.

March 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: U/W, (206) 543-1069.

March 22-24—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

April 20-21—**Ergonomics.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

May 15-17—**Occupational Hazards to Health Care Workers.** Seattle. Mon-Wed. Contact: U/W, (206) 543-1069. ◆

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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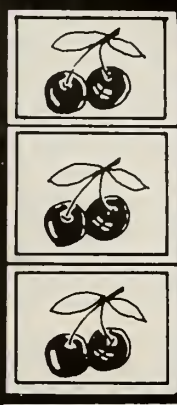

CLASSIFIED INFO (415) 882-5178

(Continued from Page 628)

PHYSICIANS WANTED

GENERAL INTERNISTS. BC/BE General Internists needed for multispecialty group. We are experiencing robust growth and are seeking Internists to join large established Department of Medicine with University affiliation. Our hospital provides integral part of University of California, Davis housestaff training program. Pleasant outpatient practice setting is in six to nine physician modules. Excellent starting salary with rapid early advancement and steady yearly salary growth thereafter. Full benefits and retirement. This is an outstanding practice opportunity. Please call Dennis Ostrem, MD, Chief of Medicine, The Permanente Medical Group, Inc, (916) 973-5781 or send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825.

RHEUMATOLOGIST. Excellent opportunity to join successful HMO practice in desirable Marin County. Contact Jonathan Freudman, MD, Assistant Chief, Department of Internal Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903; (415) 499-2357. An Equal Opportunity Employer.

INTERNIST WANTED. Dynamic, expanding Beverly Hills area group seeks two Internists capable of giving high quality, compassionate care to good mix of fee-for-service/managed-care patients. Congenial group offers competitive salary, medical/dental/malpractice/disability package, profit-sharing, and partnership potential. Respond with CV to Medical Group of Beverly Hills, 5901 W. Olympic Blvd, Ste 201, Los Angeles, CA 90036, Attn: Medical Director.

ORTHOPEDIST. One day per week. Medical-legal evaluations for traumatic injury patients. No surgery. California license required. Lucrative fee for service with high growth potential, and guaranteed base. Contact Director, PO Box 14046, San Francisco, CA 94114.

PHYSICIANS WANTED

SURGICAL ONCOLOGIST. A position is available for a well trained Surgical Oncologist to join an established multidiscipline group in Long Beach, California. Please send CV to PO Box 30, Long Beach, CA 90801.

FAMILY PRACTICE/URGENT CARE PHYSICIAN, BC/BE to staff Immediate Care Center of 35 physician multispecialty clinic in southeastern Washington. Excellent compensation and benefit package. Send CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

SACRAMENTO. BC/BE Family Physicians needed for full-time primary care clinic, part-time ER/part-time primary care clinic, or full-time in our ER. We are a large-staff model HMO offering competitive salary, excellent benefit package, and shareholder status. California license required. Contact Richard Fury, MD, 1001 Riverside Ave, Roseville, CA 95678 or call (916) 784-4620. EOE.

DIRECTOR OF DIVISION OF NEUROSURGERY. Progressive BC/BE Neurosurgeon to reorganize the Division of Neurosurgery at a major trauma and teaching center. Should be eligible for academic appointment at a major medical school. Compensation is a combination of teaching and administrative pay plus fee-for-service. Contact Francis L. Comunale, MD, Medical Director, San Bernardino County Medical Center, 780 E. Gilbert St, San Bernardino, CA 92404.

INTERNIST. Needed to establish a group practice in Redding, California. Excellent opportunity leading to a partnership. First year salary guaranteed. Must be BE/BC in Internal Medicine. Use all of your hospital and consultative skills in an area not overcrowded by subspecialists. Progressive hospital with open heart program and active ICU/CCU. Send CV to 2240 Court St, #B, Redding, CA 96001.

PHYSICIANS WANTED

EMERGENCY MEDICINE. San Francisco. Full-time position in active emergency department with housestaff training program and excellent subspecialty back-up. Competitive salary, outstanding benefits. For information call Steve Lauterbach, MD, Assistant Chief, Emergency Department, Kaiser San Francisco, (415) 929-4020.

OREGON COAST. Busy fee-for-service multispecialty group looking for additional Internist and Family Practitioner including OB to work with two Internists and three Family Practice Physicians. Well-equipped clinic next to 34-bed hospital with eight ICU/CCU beds and two new birthing rooms. Top-notch school system and just 75 miles to Portland. Send CV or call Rick Bigger at North Coast Medical Center, PC, 727 Wahanna Rd, Seaside, OR 97138; (503) 738-9551.

INTERNIST, BC/BE, California license. Group practice opportunity. Outpatient and hospital practice. Guaranteed income. Send résumé to Dr Susann J. Steinberg, Access Health Care, 26 California St, San Francisco, CA 94111.

HAVE THE BEST OF BOTH WORLDS: rural group practice, easy commute 40 minutes to larger city. Excellent clinical practice with option for close ties to academic hospitals and part-time teaching. BC/BE Family Practitioners to join with two Family Practitioners, OB/GYN, two Pediatricians, General Surgeon. Adjacent to hospital. Attractive salary/incentives. Excellent outdoor recreational opportunities. Send CV to Peter Bauer, MD, Medical Director, Family Practice Group, 255 South First East, Tooele, UT 84074; (801) 882-0423.

INTERNAL MEDICINE. San Francisco bay area—immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical housestaff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119.

RHEUMATOLOGIST. Immediate opening for BC/BE Rheumatologist with large prepaid group practice in San Francisco bay area. Busy clinical practice with opportunities for teaching and research. University appointment possible. Competitive salary. Generous benefit package. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, Permanente Medical Group, 260 International Cir, San Jose, CA 95119 or phone (408) 972-6560.

GENERAL PRACTICE. Busy medical center needs full-time physicians for urgent appointments. Significant evening and weekend hours. Abundant free time with no on-call responsibility. Excellent benefits and retirement program. Kaiser Permanente, Santa Teresa Hospital, 250 Hospital Parkway, San Jose, CA 95119; (408) 972-6180.

EMERGENCY MEDICINE, SANTA ROSA. Large HMO seeking one or more ABEM certified or eligible full-time physicians to staff emergency department in hospital presently under construction. Positions available to start January 1989, with practice primarily in San Rafael until the Santa Rosa facility opens in late 1989. Salaried position with wide range of benefits. Send inquiries to Dr John David, Chief, Department of Emergency Medicine, Kaiser Permanente, 99 Montecillo Rd, San Rafael, CA 94903; (415) 499-2400.

PALO ALTO, CALIFORNIA. Family Physician BC/BE to join nine-member department in large multispecialty group. Highly desirable location; excellent benefits. Clinical faculty appointment at Stanford available. Contact Susan D. Smith, MD, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

(Continued on Page 632)

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PHYSICIANS WANTED

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PUGET SOUND. Critical Care Internist to join four-man group. Beautiful waterfront city near Seattle. Infectious Disease experience preferred. Outstanding financial package. Send CV to Number 116, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST, with or without subspecialty, to associate with Nephrologist in coastal North Carolina. Riverfront community near beaches. 200-bed hospital with most surgical specialties. Send CV and cover letter to Number 120, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST. San Francisco bay area HMO seeks BC/BE Internist to join dynamic multispecialty group. Excellent salary and fringe benefits. Send CV and references to Dr Michael Getzell, Kaiser Permanente, 27400 Hesperian Blvd, Hayward, CA 94545.

SURGEON OPPORTUNITY. Immediate opening for General Surgeon in rural Nebraska. BC/BE. Must be licensed in Nebraska. Excellent benefits. Great hunting and fishing. Wallace & Panzer, MD, PC, 807 N. Ash St, Gordon, NE 69343; 1 (308) 282-1164.

THE ELKO REGIONAL MEDICAL CENTER is presently recruiting a Pediatrician, two Family Practitioners, and a Radiologist to assist in its growing practice. Excellent salary plus production and a comprehensive benefit package which includes profit sharing. Elko, Nevada is a rapidly growing rural community at the base of the Ruby Mountains. Outstanding recreational opportunities and school system, including a community college. Contact Cherie Atwood, Administrator, 762-14th St, Elko, NV 89801; (702) 738-3111.

SIX PHYSICIAN PRIMARY CARE GROUP seeks BC/BE Cardiologist for invasive/noninvasive practice in vacation community on Puget Sound. Practice located adjacent to community hospital, which is affiliated with Virginia Mason Medical Center in Seattle. Send CV to Harold R. Clure, MD, Fidalgo Medical Associates, PS, 24th and M Ave, Anacortes, WA 98221; or call (206) 293-3101.

EMERGENCY MEDICINE GROUP seeking career oriented ACLS, ATLS physician for immediate opening. Moderate volume; income $140,000. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to KEP, PO Box 6192, Kennewick, WA 99336; or call (509) 627-1798.

PHYSICIANS WANTED

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three-five weeks paid vacation; seven paid holidays; malpractice, medical, dental and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall 1988. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

PACIFIC NORTHWEST

The Wenatchee Valley Clinic, a multispecialty group of 105 physicians, has several practice opportunities throughout its seven practice locations. Currently we are seeking:

MAIN FACILITY—WENATCHEE

- Allergy
- ENT
- Nephrology
- Psychiatry
- Infectious Disease
- Neurology
- Neurosurgery
- Orthopedics

SATELLITE FACILITIES—OMAK/MOSES LAKE

- Orthopedics
- Dermatology
- OB/GYN

All positions offer an excellent compensation and benefit package. North central Washington provides a high quality of life for those interested in an abundance of recreational opportunities in a family-oriented rural setting. If interested, send your CV to Dr Gerald Gibbons, Medical Director, Wenatchee Valley Clinic, 820 N. Chelan Ave, Wenatchee, WA 98801, or call (509) 663-8711, ext 205.

ENDOCRINOLOGIST. Full- or part-time to join long established practice, San Francisco bay area, California. Reply Number 126, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTITIONER, BC/BE. Excellent opportunity to practice with the largest community health plan in San Francisco bay area. A full-time position with a multidisciplinary team approach to patient care. Call (408) 262-7944, ext 207.

SAN FRANCISCO BAY AREA multispecialty group seeks Neurologist, BC/BE, to join 24 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

PEDIATRICIAN, BC/BE. Excellent opportunity to practice with the largest community health plan in San Francisco bay area. A full-time position with a multidisciplinary team approach to patient care. Call (408) 262-7944, ext 207.

SAN FRANCISCO BAY AREA multispecialty group seeks Internist, BC/BE, to join 24 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

SURGEON, BC/BE. Excellent opportunity to practice with the largest community health plan in San Francisco bay area. A full-time position with a multidisciplinary team approach to patient care. Call (408) 262-7944, ext 207.

PHYSICIANS WANTED

OCCUPATIONAL/FAMILY PRACTICE. The Pacific Northwest's leading outpatient medical provider has career opportunities for Primary Care Physicians to join an expanding 150 person medical group. Full/part-time openings throughout California and Seattle-Tacoma, Washington. Prior outpatient/occupational experience preferred. Attractive package includes competitive base salary plus incentive program, malpractice insurance, comprehensive benefits, 401(k) plan, vacation/sick/holiday/CME. Opportunity for advancement for energetic, hard-working physician committed to quality health care. Join our dynamic team of health care professionals. Contact Robin Smith, Director, Personnel, Readi-Care/CHEC, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (408) 737-8531, (800) 237-3234.

NEUROLOGIST, BC/BE, full/part-time, for expanding San Francisco bay area private practice with emphasis on Occupational Neurology and med-legal evaluations. Expertise in EMG, EEG, and EP desired. Excellent reputation, referral base, facilities, and support staff. CV and letter stating professional goals, availability to 4017 24th St, Ste #7, San Francisco, CA 94114.

FAMILY PRACTICE/SACRAMENTO. Due to continued growth, positions for Family Practice are now available at Kaiser Permanente Medical Center, south Sacramento. Our salary is very competitive and we have an outstanding retirement and benefits package. Your practice at Kaiser will allow insulation from the headaches and financial uncertainty of private office practice, while fostering your professional growth at a first rate medical center. For further information, please contact Jack Berger, MD, Assistant Chief, Department of Medicine, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento, CA 95823; or call (916) 686-2267.

PEDIATRICIAN. 30 member multispecialty private practice group in San Francisco bay area is seeking additional physician to join its Department of Pediatrics. Excellent opportunity in fast growing community. Salary and incentive, plus full benefit package. Must be BE/BC. Send CV to Michael E. Sondel, CEO, Family Doctor Medical Group, 1617 Broadway, Vallejo, CA 94589; (707) 553-6023.

OB/GYN. 30 member multispecialty private practice group in San Francisco bay area is seeking additional physician to join its Department of Obstetrics and Gynecology. Excellent opportunity in fast growing community. Salary and incentive, plus full benefit package. Must be BE/BC. Send CV to Michael E. Sondel, CEO, Family Doctor Medical Group, 1617 Broadway, Vallejo, CA 94589; (707) 553-6023.

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for two BC/BE Family Practitioners to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1550 Gateway Blvd, Fairfield, CA 94533; (707) 427-4000.

FAMILY PRACTICE/GENERAL PRACTICE Physician wanted for full-time practice to work three days a week and share with another practitioner. Rural setting, good pay, nice people. Can commute for two nights a week, one hour Sacramento, one hour 15 minutes Nevada City, two hours San Francisco. Contact Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

WELL ESTABLISHED HMO located in northern California wine country seeking General Internists. Attractive salary, benefits, and security. Please send CVs to Rich Zweig, MD, 401 Bicentennial Way, Santa Rosa, CA 95403.

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PHYSICIANS WANTED

KAISER PERMANENTE

Good People. Good Medicine.

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most subspecialties. We are a young aggressive group in a well known HMO organization with excellent benefits and a very reasonable call schedule. You will enjoy the patient population with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, Kaiser Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

PACIFIC NORTHWEST—INTERNIST. There are three busy solo Internists, practicing near our 155-bed hospital in Tacoma, Washington, who are seeking associates. They prefer candidates with interest in Geriatrics. Send your CV to Manager, Professional Relations, Humana Inc, Dept HH-11, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

INTERNISTS AND CARDIOLOGIST for busy, expanding, well-established multispecialty HMO with adjacent hospital. Liberal fringe benefits, competitive salary. Send CV to Mark Cole, MD, Permanente Medical Group, 1200 El Camino Real, South San Francisco, CA 94080.

SONOMA AND LAKE COUNTIES. Immediate openings for Emergency Physicians who desire to live in the wine country north of San Francisco. Prefer BC/BP Emergency Physicians, but will consider BC in Family Practice, Internal Medicine, or Surgery in conjunction with Emergency Medicine experience. Low/moderate volume ED's or in combination with satellite ACC. Guaranteed $90-$100,000 per year; paid malpractice. Contact Richard Gillespie, MD, Redwood Empire EM Group, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

OREGON. General Internist sought for busy practice. 10 member multispecialty group. Beautiful rural community. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

URGENT CARE PHYSICIANS. The Hubert H. Humphrey Comprehensive Health Center and the H. Claude Hudson Comprehensive Health Centers, Los Angeles, California, primary care public health components of the Los Angeles County Department of Health Services, are seeking applicants for their Urgent Care Centers and Adult Medical Clinic staff. Applicants for the planned Urgent Care Centers should be BE/BC in one of the following specialties: Family Medicine, Emergency Medicine, Internal Medicine, Pediatrics, Pathology, Orthopedics, Cardiology, Radiology, and OB/GYN and have Advanced Cardiac Life Support certification. Qualified physicians wishing to work in a unique and challenging environment with exposure to a dynamic, growing, Ambulatory Care and Public Health System, please send CV to William M. Brown, MD, Medical Director (Acting), Hubert H. Humphrey Comprehensive Health Center, 5850 S. Main St, Los Angeles, CA 90003; (213) 235-7212; and Carol Henneman, MD, H. Claude Hudson Comprehensive Health Center, 2829 S. Grand Ave, Los Angeles, CA 90007; (213) 744-3750.

PHYSICIANS WANTED

OREGON
Internal Medicine

Excellent opportunities for BC/BE General Internists for immediate and mid-1989 openings in the Portland area. Large multispecialty group provides professional services for 320,000 members of Kaiser Permanente, Northwest Region. Beautiful recreation area with easy access to mountains and beaches. Competitive salary and benefits; shareholder eligibility after two years. Forward inquiry and CV to:

Fred M. Nomura, MD
Regional Medical Director
Northwest Permanente, P.C.
3600 N. Interstate Ave
Portland, OR 97227

INTERNIST/NEPHROLOGIST with special interest in teaching Internal Medicine for full-time appointment in university-affiliated, active teaching and clinical program with part-time Nephrology private practice. Inquiries, including CV, should be sent to A. G. Kavalich, MD, Director, Nephrology, San Bernardino County Medical Center, 780 E. Gilbert St, San Bernardino, CA 92404.

PEDIATRICIAN, BC/BE. Join Pediatrician and Nurse Practitioner in growing, quality practice near Sacramento, California. Excellent professional opportunity. Good cultural setting and quality of life. Progressive community hospital. Send CV to Number 124, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA, REDWOODS RESORT COMMUNITY. Needs a semi-retired MD who is looking to share a practice part-time with fellow semi-retired MD who's interested in working part-time, fishing, golfing, and spending quality time with family. If you're looking for sunshine, a country atmosphere, and a small practice contact Number 127, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OREGON COAST. BC/BE Family Practice Physician to join four Family Practitioners in multispecialty group. Full spectrum of Family Practice, optional OB. New clinic near hospital. Contact Mrs Jackie Crowder, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151 ext 294, or 1 (800) 234-1231.

NORTH IDAHO. Family Physician needed to join four physician group. College and two state universities within the locality. Area provides abundant outdoor recreational opportunities. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501.

WELL ESTABLISHED HMO located in northern California wine country seeking General Internists. Attractive salary, benefits, and security. Please send CVs to Rich Zweig, MD, 401 Bicentennial Way, Santa Rosa, CA 95403.

PSYCHIATRIST POSITION AVAILABLE (BC/BE) for varied and interesting out-patient mental health department. This department is part of a multispecialty group practice located at a comprehensive medical center. Department sees a diverse client group including military, dependents, and retirees. Duties include clinical consultation, evaluation, psychotherapy, and prescription. Contact Dan O'Connell, PhD, Program Director, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4045.

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
5414 E. Montecito, Fresno, CA 93727.
Or call (209) 252-3047.

MODESTO, CALIFORNIA community clinic is recruiting a Primary Care Physician to serve farm workers and other underserved people, including the homeless. Excellent location in city of 180,000, one and one-half hours from Yosemite and the bay area. Please contact Michael Sullivan, Merced Family Health Centers, Inc, PO Box 858, Merced, CA 95341; (209) 383-1848.

FIVE PERSON INTERNAL MEDICINE GROUP seeking BC/BE Pulmonologist, intensive care bronchoscopy training. Sierra Foothills, California. Reply to Number 122, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED IN TEXAS AND OKLAHOMA. Major cities to rural communities. Cardiology, ENT, Family Practice, General Surgery, Internal Medicine, OB/GYN, Oncology, Orthopedic Surgery, Pulmonology, Pediatrics, Psychiatry, Radiology, Urology. Excellent quality of life, excellent compensation, etc. Reply with CV to Armando L. Frezza, Medical Support Services, 8806 Balcones Club Dr, Austin, TX 78750; office (512) 331-4164, 24-hour FAX (512) 331-6741.

HIRING! Federal government jobs in your area and overseas. Many immediate openings without waiting list or test. $15,000 to $68,000. Phone call refundable. (602) 838-8885 ext 9947.

NORTHERN CALIFORNIA, REDWOOD COAST. Opening for Emergency Room Physician at expanding 78-bed hospital with 12,000 visits per year. Independent contractor status, paid occurrence malpractice. University community, excellent schools, abundant cultural and outdoor activities, served by major airlines. Contact Number 128, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CARDIOLOGIST—ARIZONA. A regionally recognized 15 physician Cardiology group in Phoenix is now seeking to add one non-invasive and two invasive Cardiologists. Their new offices are located adjacent to our 314-bed hospital there. Send your CV to Manager, Professional Relations, Humana Inc, Dept HH-11, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

NEVADA. Family Practice, Internal Medicine, Pediatrics, OB/GYN, Radiology. Immediate openings in several rural communities; guaranteed salary, full benefits including paid malpractice, and possible University affiliation. No fee to applicant. Contact Sherry Semiatin, Office of Rural Health, Reno, NV 89557-0046; (702) 784-4841.

HEMATOLOGIST/ONCOLOGIST, WASHINGTON STATE BC/BE. Immediate opportunity to take over established practice within the Hematology/Oncology (three and one-half physician) Division of the Rockwood Clinic, a 60 member multispecialty group. Competitive salary and benefits leading to early shareholder status. Spokane (metropolitan population 350,000) offers affordable housing, excellent schools, cultural activities, and unlimited outdoor recreation. Send CV to Colleen Mooney, Recruitment Coordinator, Rockwood Clinic, TAF C-13, Spokane, WA 99220-4013; (509) 448-1304.

INTERNIST, BC/BE. Excellent opportunity to practice with the largest community health plan in San Francisco bay area. A full-time position with a multidisciplinary team approach to patient care. Call (408) 262-7944, ext 207.

(Continued on Page 637)

A BETTER CHANCE FOR

AN ULCER-

Well-controlled clinical trials confirm:

ZANTAC 150 mg hs significantly superior to cimetidine 400 mg hs for maintenance therapy in healed duodenal ulcers.

FREE FUTURE

Percent of patients ulcer-free after 1 year of therapy

ZANTAC 150 mg hs (n = 60)	**84%***
cimetidine 400 mg hs (n = 66)	**57%**
ZANTAC 150 mg hs (n = 243)	**77%†**
cimetidine 400 mg hs (n = 241)	**63%**

*P = 0.01 †P = 0.0004 % life-table estimates

All patients were permitted prn antacids for relief of pain.
Adapted from Silvis[1] and Gough.[2]

These two trials[1,2] used the currently recommended dosing regimen of cimetidine (400 mg hs) and ranitidine (150 mg hs). A comparison of other dosing regimens has not been studied.
The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid.
The superiority of ranitidine over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets hs

Glaxo/ ROCHE

See next page for references and Brief Summary of Product Information.

References: 1. Silvis SE, Griffin J, Hardin R, et al: Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol* 1985;7(6):482-487. 2. Gough KR, Korman MG, Bardhan KD, et al: Ranitidine and cimetidine in prevention of duodenal ulcer relapse: A double-blind, randomised, multicentre, comparative trial. *Lancet* 1984;2:659-662.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

May 1988

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(Continued from Page 633)

PHYSICIANS WANTED

PATHOLOGIST, APCP, desired for aggressive three man group with demanding, busy, interesting practice. Must have or be willing to rapidly develop a forte in Microbiology. Pacific/Rocky Mountain Northwest with abundant outdoor activities and competitive income. Please reply to Number 123, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN FRANCISCO BAY AREA multispecialty group seeks Family Practitioner, BC/BE, to join 24 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

RHEUMATOLOGIST. BC/BE wanted to join solo certified Rheumatologist with group coverage in large southern California private-pay Rheumatology practice. Salary plus bonus with association and investment opportunity. Lab, x-ray, and physical therapy. Clinical research and teaching opportunities. Send CV to R. S. Gordon, MD, FACP, Arthritis Medical Clinic, 5945 Brockton Ave, Riverside, CA 92506; or call (714) 781-7700.

FAMILY PRACTICE OR INTERNIST to associate with busy family practice in Tulare, California. Large office established for 30 years with x-ray, lab, etc. Excellent living and practice environment. (209) 686-8611.

SUN VALLEY—Internist to practice Primary Care with two Internists in quality multispecialty group. Well equipped hospital. High quality of life with outstanding year 'round recreation presents unique opportunity and professional challenge. CV and references with first letter please. Tom Peterson, PO Box 66, Sun Valley, ID 83353-0066; (208) 622-4526.

CARDIOLOGIST, BC/BE, PACIFIC NORTHWEST. Strong need for additional invasive Cardiologist in solid, high quality medical community. Excellent lifestyle and area. Excellent opportunity. Please include CV with reply to Number 129, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE NEUROLOGIST to join progressive San Francisco bay area HMO. Busy clinical practice in desirable Marin County. Competitive income and excellent benefits. Please contact Jonathan Freudman, MD, Assistant Chief, Department of Internal Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903. AA/EOE employer.

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee for service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

ORTHOPEDIST. One day per week. Medical-legal evaluations for traumatic injury patients. No surgery. California license required. Lucrative fee for service with high growth potential and guaranteed base. Contact Director, PO Box 14046, San Francisco, CA 94114.

PHYSICIAN, STUDENT HEALTH SERVICE, SAN JOSE STATE UNIVERSITY. Ambulatory health care facility providing primary health care services to 27,000 students (225 patients per day). Medical staff of 10 Physicians and three Nurse Practitioners. Two 10-month Physician positions available. BC in Internal, Emergency Medicine, Family Practice, and Pediatrics/Adolescent Medicine. Send CV to Department of Human Resources, San Jose State University, One Washington Sq, San Jose, CA 95192-0046.

SAN FRANCISCO—INTERNIST or FAMILY PRACTITIONER. Full- or part-time association with General Internist—15 years established practice—light on call; malpractice provided; fringe benefits; incentive option. Send CV to Martin Lorber, MD, 1500 Southgate Ave, Daly City, CA 94015; or call (415) 992-4466.

PHYSICIANS WANTED

VA MEDICAL CENTER, PRESCOTT, ARIZONA
is recruiting for a BC Psychiatrist with administrative ability to function as Chief of Psychiatry Service. Salary range is $70,000 to $80,000 depending on qualifications. Prescott is a 200-bed medical facility with an active Alcohol Dependency Treatment Program. Prescott is located in the north central mountains of Arizona with a population of 25,000. Send CV to **F. C. Lepperd, Jr, MD, Chief of Staff, VA Medical Center, Prescott, AZ 86313; or call (602) 445-4860 ext 301.** Equal Opportunity Employer.

LOS ANGELES (Los Angeles County)—55 physician multispecialty Medical Group seeks full-time BC/BE Physicians in the following specialties: Cardiology, ENT, Family Practice, Infectious Disease, and Rheumatology. Please send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004; (213) 386-8440.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

VENTURA (Ventura County). Multispecialty group of 40 physicians has immediate positions available for BC/BE General Internist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist, 2705 Loma Vista Rd, Ventura, CA 93003.

VENTURA (Ventura County). Multispecialty group of 40 physicians has immediate position available for BC/BE Internist/Pulmonologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist/Pulmonologist, 2705 Loma Vista Rd, Ventura, CA 93003.

VENTURA (Ventura County). Multispecialty group of 40 physicians has immediate position available for BC/BE Cardiologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Cardiologist, 2705 Loma Vista Rd, Ventura, CA 93003.

VENTURA COUNTY. Multispecialty group of 40 physicians has immediate positions available for two BC/BE Family Practitioners. These openings are located in the main facility in Ventura and the Camarillo and Oxnard satellite offices. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Family Practitioner, 2705 Loma Vista Rd, Ventura, CA 93003.

FAMILY PRACTICE, PUGET SOUND. 23 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to Carol Larsen, Acting Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

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Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.
Contact Carol Sweig, Director, (415) 673-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for two BC/BE Family Practitioners to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1550 Gateway Blvd, Fairfield, CA 94533; (707) 427-4000.

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BC GENERAL INTERNIST. Currently Chief of federal outpatient clinic with clinical and administrative responsibilities. Previous private practice experience. Seeks Ambulatory Care position in southern Nevada or southern California. Reply to Number 125, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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THRIVING SURGICAL PRACTICE for sale due to untimely death of physician. Sale price negotiable. Active progressive medical community in beautiful central Washington. Excellent community hospitals. Wonderful family outdoor environment. (509) 453-5752; 1111 W. Spruce, #30, Yakima, WA 98902.

FAMILY PRACTICE. Outstanding opportunity for a Family Practice couple or two Family Practice Physicians to purchase a well established practice in northern California near Sacramento. The practice includes equipment, nicely appointed office, large patient volume, and excellent staff. Negotiable terms. Please call collect Physician Relations Manager, (916) 537-5009.

GREAT OPPORTUNITY—No money down. Cardiology/Internal Medicine practice for sale in Claremont. Great income potential for right MD. Write to PO Box 2836, Wrightwood, CA 92397.

SAN DIEGO—OB/GYN—PEDIATRIC AND OTHER SPECIALTY PRACTICES AVAILABLE. Long established—doctors retiring. Various prices—low down payments. CBI (619) 283-7009.

FAMILY PRACTICE PHYSICIAN WANTED. To replace retiring physician in Clarkston, Washington. Office located adjacent to Tri-State Memorial Hospital. Hospital guarantees income of $5,000 per month first year. Doctor interested in selling office equipment. Contact Dr Ralph Haas, Jr, at (509) 758-7121.

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(Continued on Page 641)

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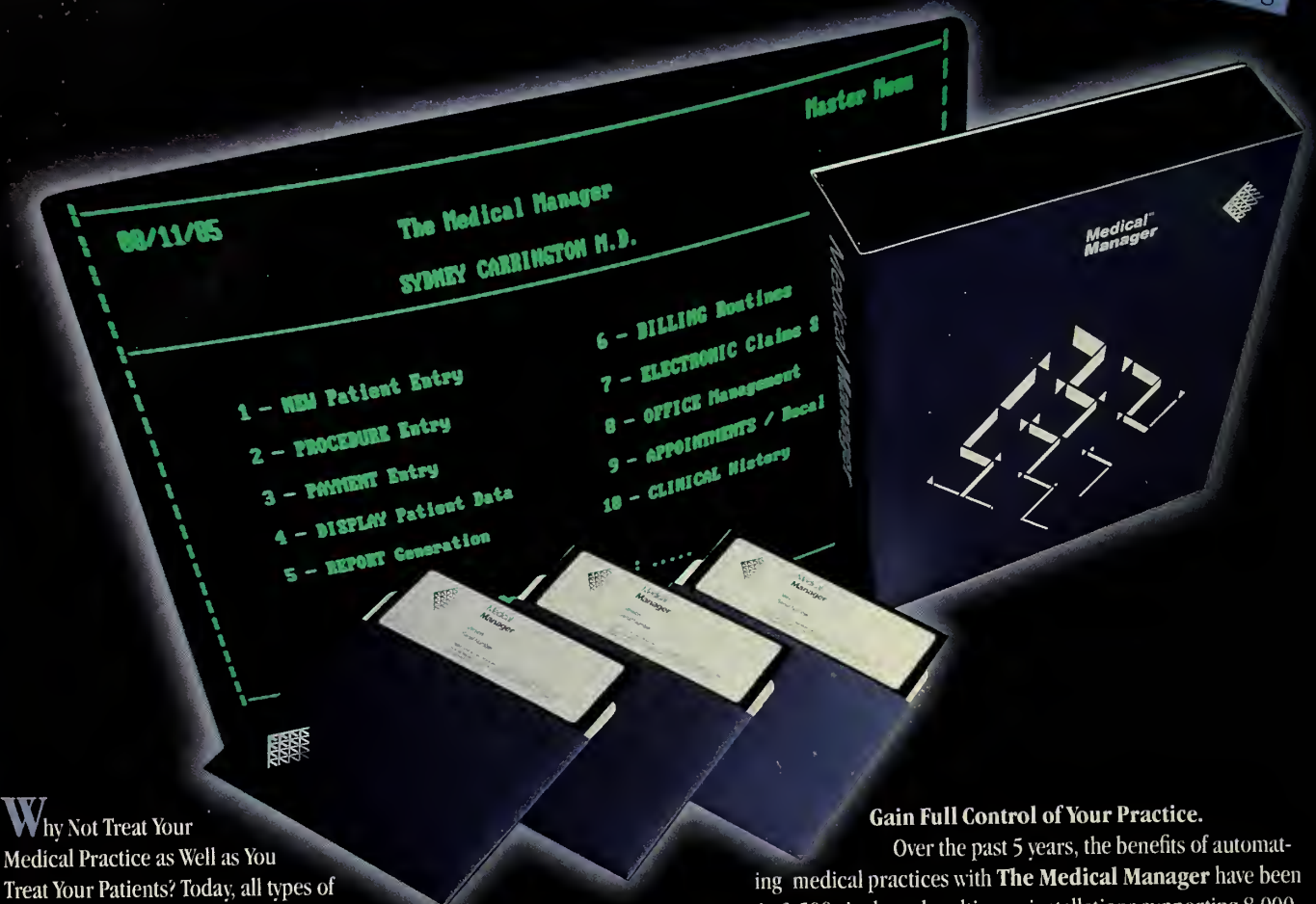

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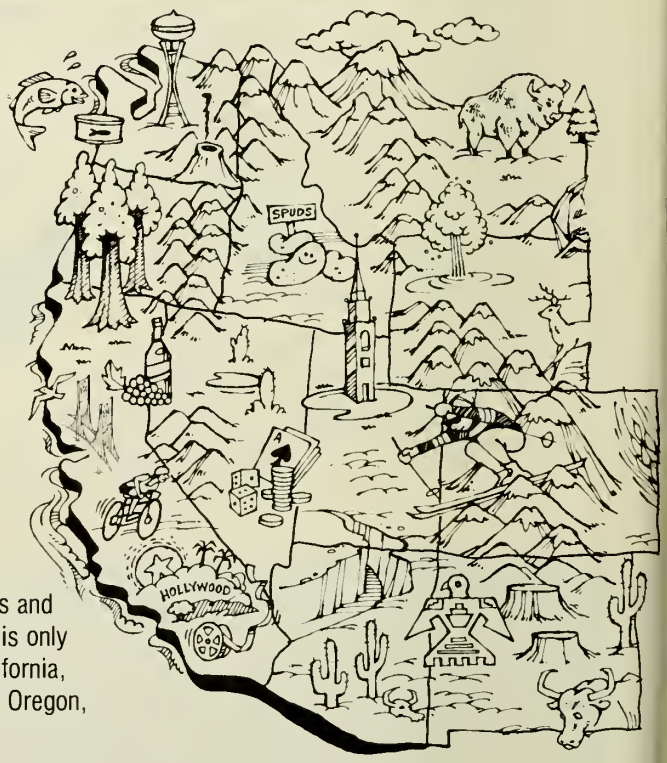

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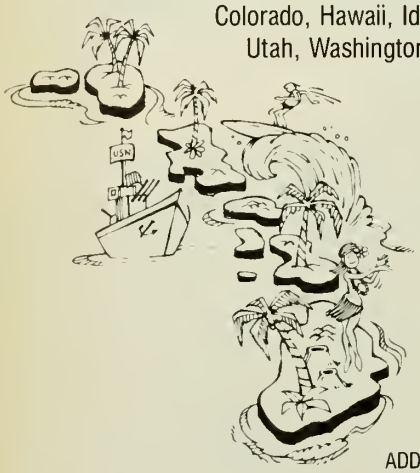

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1989, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1989, date and place to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1989, date and place to be announced.

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Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1989, date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 1-4, 1989, Ely.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 11-14, 1989, Holiday Inn Pyramid, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1988, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1989, date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1989, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1989, date and place to be announced.

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Rocephin® IV·IM

ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae, Streptococcus* species (excluding enterococci), *Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus, Staph. epidermidis, Streptococcus* species (excluding enterococci), *E. cloacae, Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii* and *Klebsiella* species (including *K. pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph. aureus, Strep. pneumoniae, Streptococcus* species (excluding enterococci), *E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae*

MENINGITIS caused by *H. influenzae, N. meningitidis* and *Strep. pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli*

SURGICAL PROPHYLAXIS: Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (e.g., during coronary artery bypass surgery)

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery. When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure

SUSCEPTIBILITY TESTING: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients. This appears to be reversible on discontinuation of therapy. In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens. Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease, consider conservative management

PRECAUTIONS: *GENERAL*: Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum

ROCEPHIN® (ceftriaxone sodium/Roche)

duration of animal toxicity studies was six months

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section. *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Exercise caution before administration to hyperbilirubinemic neonates, especially prematures

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e.g., dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone, piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone, bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION)

Also supplied as a sterile crystalline powder as follows

ADD-Vantage Vials** containing 1 gm or 2 gm equivalent of ceftriaxone

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.9 gm dextrose hydrous, USP added

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.2 gm dextrose hydrous, USP added

NOTE: Rocephin in the frozen state should not be stored above -20°C

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†Manufactured for Roche Laboratories, Division of Hoffmann-La Roche Inc., by Travenol Laboratories, Inc., Deerfield, Illinois 60015

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ceftriaxone sodium/Roche

Please see adjacent page for summary of product information.

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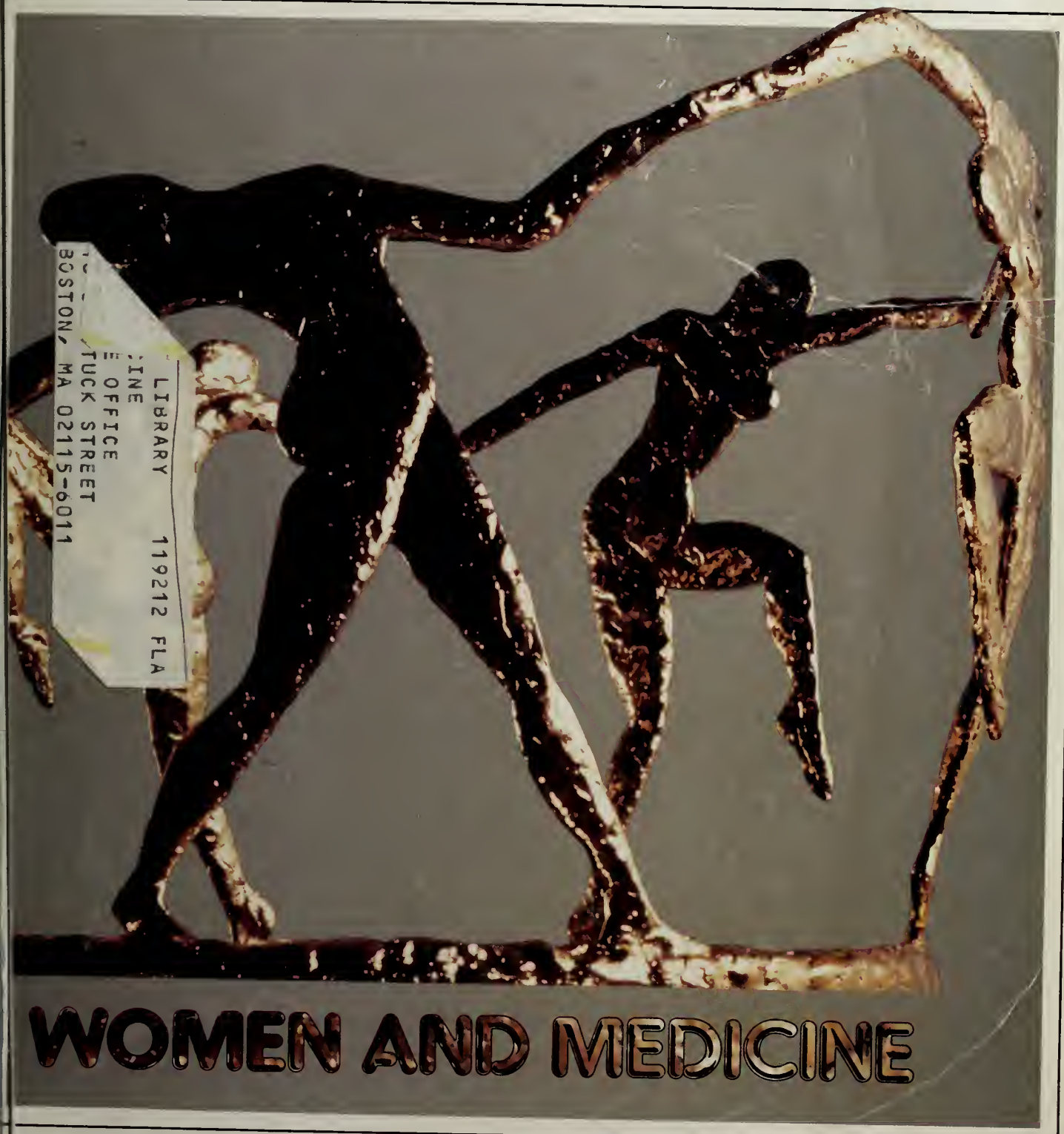

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Please see reference and Brief Summary of Prescribing Information on next page.

Glaxo/ ROCHE

Reference: 1. Sontag S, Robinson M, McCallum R, et al: Ranitidine therapy for gastroesophageal reflux disease. Results of a large double-blind trial. *Arch Intern Med* 1987;147:1485-1491.

ZANTAC® 150 Tablets (ranitidine hydrochloride) **ZANTAC® 300 Tablets (ranitidine hydrochloride)** **BRIEF SUMMARY**

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

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Dr. Holwick outside of hospital where she practices as a civilian traumatologist.

Dr. Holwick in operating room at Letterman Army Medical Center.

JANN L. HOLWICK, M.D.

General and Trauma Surgeon.
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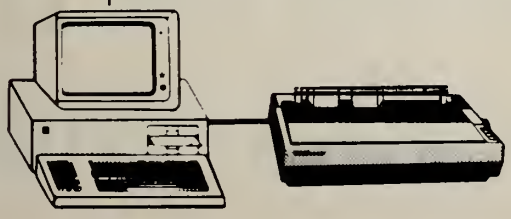

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over sculpture, The Witches M by Sandra Shannonhouse, 100 East E Street, Benicia, CA 94510; cover design by Celeste Rusconi

IN HYPERTENSION*

QUALITY

***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

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1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.

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Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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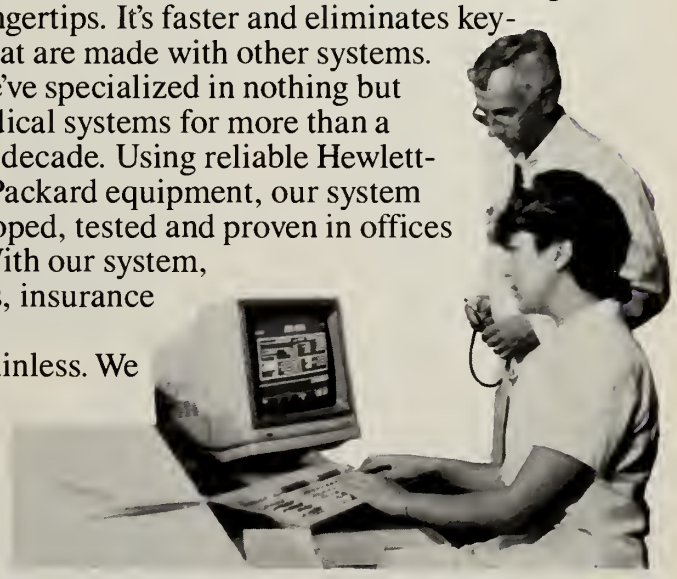

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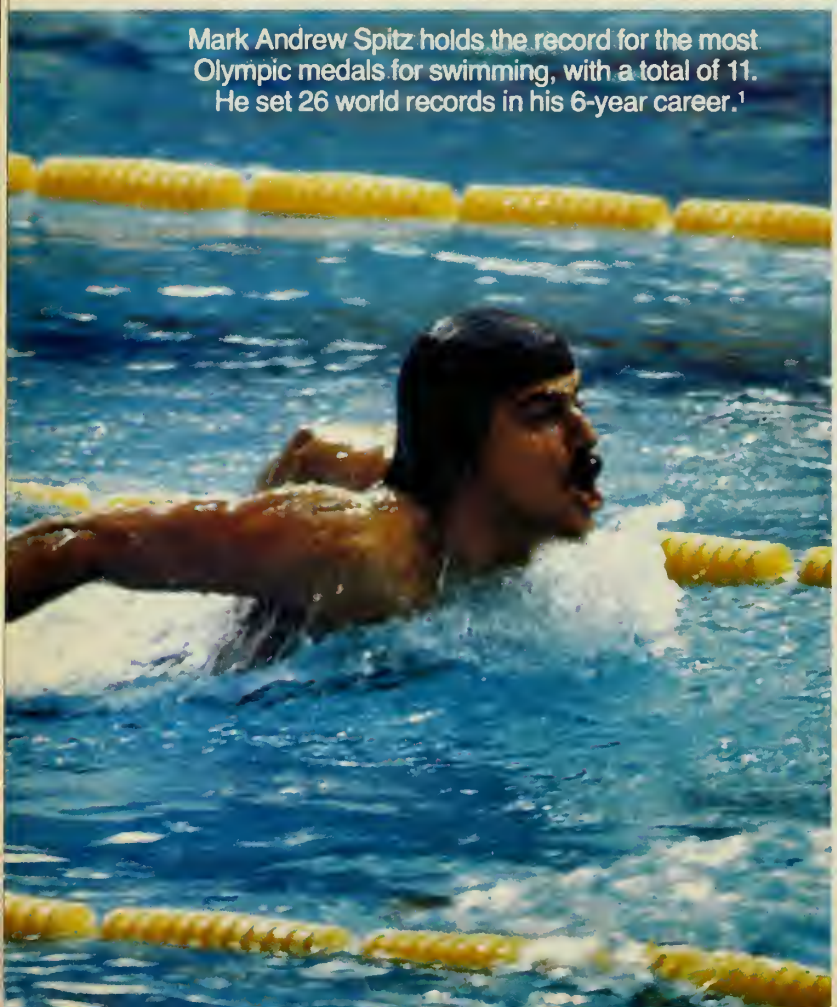
Mary Lou Retton set the record for longest uninterrupted possession of the American Cup by a female gymnast.[1]



Mark Andrew Spitz holds the record for the most Olympic medals for swimming, with a total of 11. He set 26 world records in his 6-year career.[1]

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PLEASE SEE FULL PRESCRIBING INFORMATION.

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than 1 year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer-reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5-13.9 times greater than in nonusers. The risk appears to depend both on duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that women who had been exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (30-90%) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data on the use of other estrogens are not available, it cannot be presumed they would not induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb-reduction defects. One case control study estimated a 4.7-fold increased risk of limb-reduction defects in infants who had been exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses.

If Estraderm is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus and of the advisability of continuation of the pregnancy.

INDICATIONS AND USAGE

Estraderm is indicated for the treatment of the following moderate-to-severe vasomotor symptoms associated with menopause; female hypogonadism; female castration; primary ovarian failure; and atrophic conditions caused by deficient endogenous estrogen production, such as atrophic vaginitis and kraurosis vulvae.

CONTRAINDICATIONS

Estrogens should not be used in women or men with any of the following conditions:

1. known or suspected cancer of the breast,
2. known or suspected estrogen-dependent neoplasia;
3. known or suspected pregnancy (see Boxed Warning);
4. undiagnosed abnormal genital bleeding,
5. active thrombophlebitis or thromboembolic disorders;
6. history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use

WARNINGS

1. *Induction of Malignant Neoplasms.* Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.)

At the present time, there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of breast cancer, although a recent long-term follow-up of a single physician's practice has raised this possibility. Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

2. *Gallbladder Disease.* A recent study has reported a two- to threefold increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving oral estrogens, similar to the twofold increase previously noted in users of oral contraceptives.

3. *Effects Similar to Those Caused by Estrogen-Progestogen Oral Contraceptives.* There are several serious adverse effects of oral contraceptives and other high-dose oral estrogen treatments, most of which have not, up to now, been documented as consequences of postmenopausal estrogen replacement therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women.

a. *Thromboembolic Disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found, this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore, estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

b. *Hepatic Adenoma.* Benign hepatic adenomas have been associated with the use of oral contraceptives. Although benign and rare, these tumors may rupture and cause death from intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations, but they should be considered if abdominal pain and tenderness, abdominal mass, or hypovolemic shock occurs in patients receiving estrogen. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The causal relationship of this malignancy to these drugs is not known.

c. *Elevated Blood Pressure.* Women using oral contraceptives sometimes experience increased blood pressure which, in most cases, returns to normal upon discontinuing the drug. There is now a report that this may occur with use of oral estrogens in the menopause and blood pressure should be monitored with estrogen use, especially if high doses are used. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol does not affect renin substrate.

d. *Glucose Tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

4. *Hypercalcemia.* Administration of high doses of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures should be taken to reduce the serum calcium level.

PRECAUTIONS

General

1. A complete medical and family history should be taken before initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, as well as a cervical Papanicolaou test. As a general rule, estrogen should not be prescribed for longer than 1 year without another physical examination being performed.
2. Because estrogens may cause some degree of fluid retention, careful observation is required when conditions that might be influenced by this factor are present (e.g., asthma, epilepsy, migraine, and cardiac or renal dysfunction).
3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as uterine bleeding, mastodynia, etc.
4. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Estrogens should be used with caution in patients who have or have had endometriosis.
5. Studies of the addition of a progestin for 7 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 12 to 13 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks that may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The choice of progestin and dosage may be important in minimizing these adverse effects.
6. Oral contraceptives appear to be associated with an increased incidence of mental depression. Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.
7. Preexisting uterine leiomyomata may increase in size during prolonged estrogen use. If this occurs, estrogen therapy should be discontinued while the cause is investigated.
8. In patients with a history of jaundice during pregnancy, there is an increased risk that jaundice will recur with the use of estrogen-containing oral contraceptives. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.
9. Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients.
10. Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Information for Patients

See Patient Package Insert printed below.

Drug/Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following changes have been observed with large doses of oral estrogen:

1. increased sulfobromophthalein retention,
2. increased prothrombin time; increased factors VII, VIII, IX, and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability;
3. increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay; free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered; TBG was not affected in clinical trials of Estraderm;
4. reduced response to the metyrapone test;
5. reduced serum folate concentration;
6. increased serum triglyceride and phospholipid concentration, and decreased pregnanediol excretion.

The pathologist should be informed that the patient is receiving estrogen therapy when relevant specimens are submitted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

See WARNINGS and Boxed Warning.

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver.

Pregnancy Category X

See CONTRAINDICATIONS and Boxed Warning.

Estrogens should not be used during pregnancy.

Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS

See WARNINGS and Boxed Warning regarding potential adverse effects on the fetus, induction of malignant neoplasms, increased incidence of gallbladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.

The most commonly reported adverse reaction to Estraderm in clinical trials was redness and irritation at the application site. This occurred in about 17% of the women treated and caused approximately 2% to discontinue therapy. Reports of rash have been rare.

The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

Genitourinary System: Breakthrough bleeding, spotting, change in menstrual flow; increase in size of uterine fibromyomata; change in cervical erosion and amount of cervical secretion.

Endocrine. Breast tenderness, breast enlargement.

Gastrointestinal: Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice have been observed with oral estrogen therapy.

Eyes. Steepening of corneal curvature; intolerance to contact lenses.

Central Nervous System: Headache, migraine, dizziness.

Miscellaneous: Change in weight, edema, change in libido.

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*See DESCRIPTION

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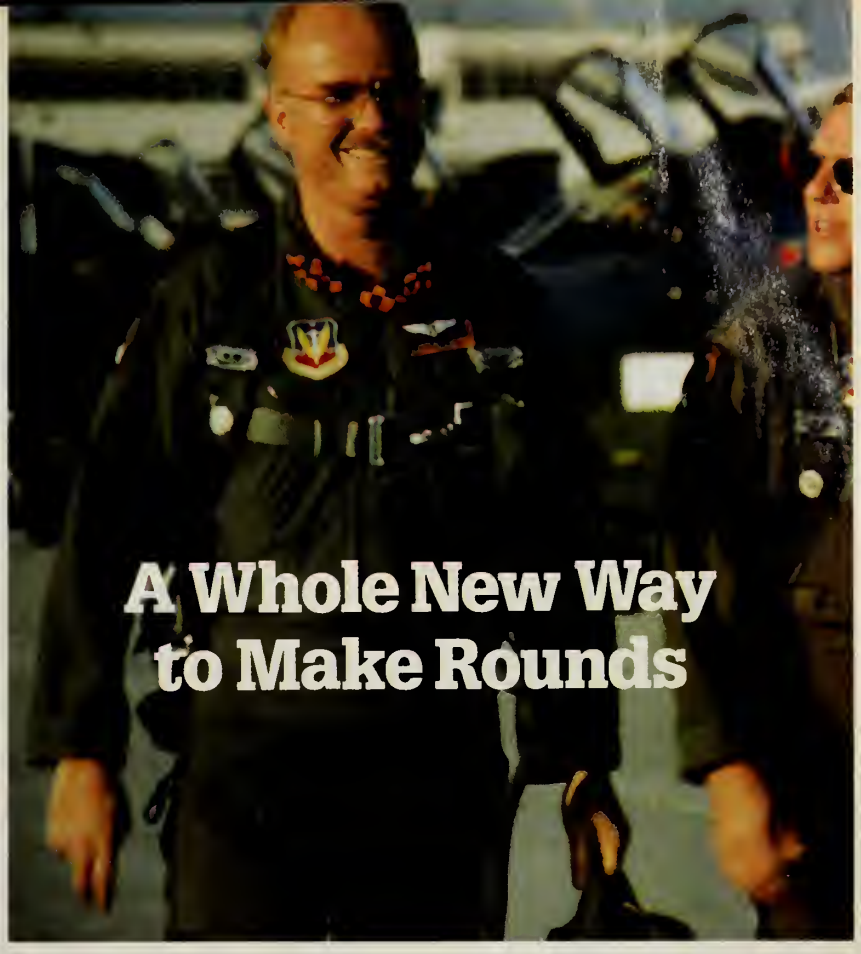

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Specialty	Composite* Insurance Companies	CAP/MPT	Savings with CAP/MPT	Composite* Insurance Companies	CAP/MPT	Savings with CAP/MPT
Psychiatry	$ 5,100	$ 2,365	54%	$ 3,789	$ 2,052	46%
Pediatrics	7,357	2,365	68%	6,208	2,052	67%
Urology	18,571	13,735	26%	14,560	11,776	19%
Anesthesiology	19,704	13,735	30%	16,299	11,776	28%
General Surgery	30,841	17,853	42%	22,388	15,306	32%
Plastic Surgery	31,557	17,853	43%	22,961	15,306	33%
Orthopedic Surgery w/Spinal	39,744	21,971	45%	34,184	18,837	45%
Obstetrics/ Gynecology	49,812	21,971	56%	40,220	18,837	53%

* Insurance company composite rates are averages based upon 4/1/88 rates of The Doctors' Company, 6/1/87 rates of MIEC, 1988 rates of Norcal and SCPIE. Details of source data on request. No costs shown here for San Diego or Imperial County. Other surcharges, credits, reductions may apply. All costs based on mature rate (including retroactive coverage).

CAP/MPT costs are based on dues and January 1988 mature assessments. They do not include the $200 membership fee and refundable initial trust contribution amounts.

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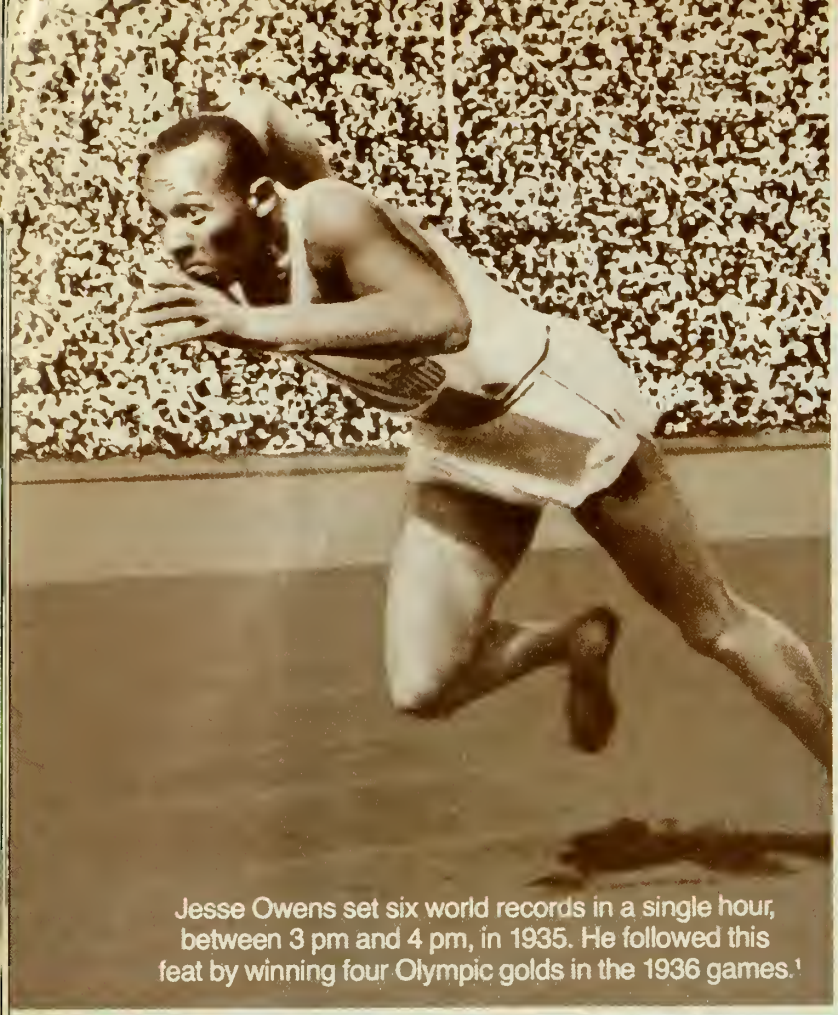
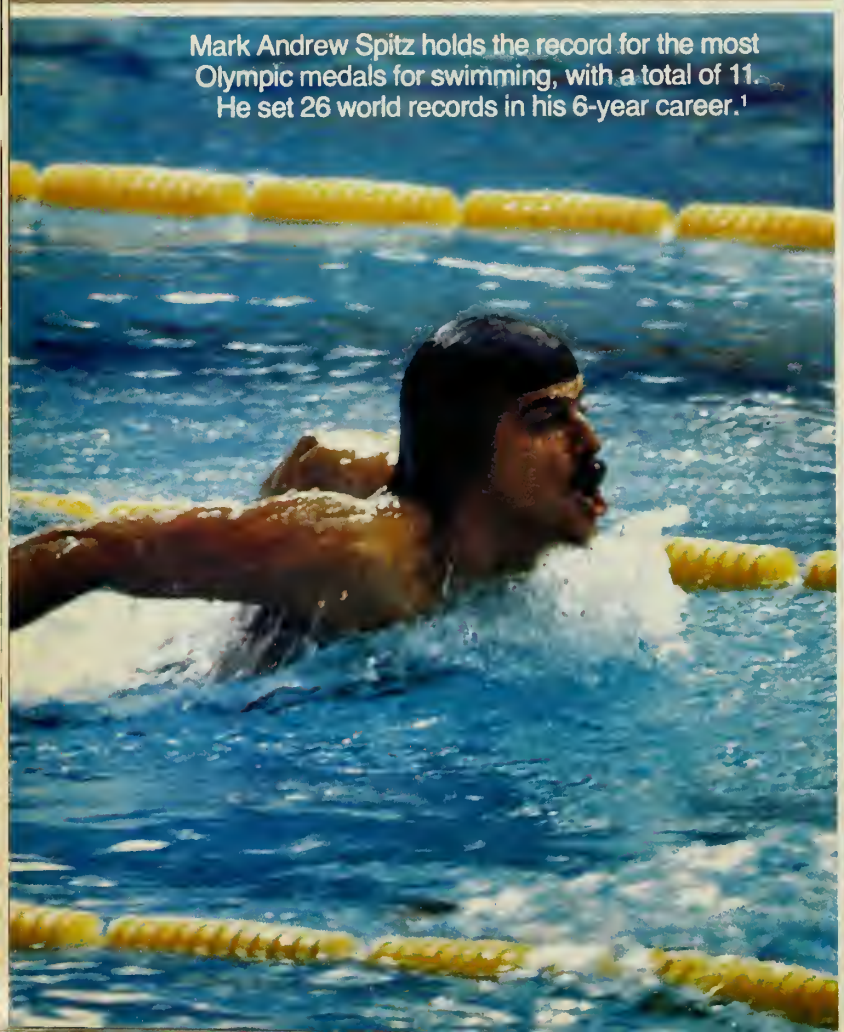


Jesse Owens set six world records in a single hour, between 3 pm and 4 pm, in 1935. He followed this feat by winning four Olympic golds in the 1936 games.[1]

Mary Lou Retton set the record for longest uninterrupted possession of the American Cup by a female gymnast.[1]



Mark Andrew Spitz holds the record for the most Olympic medals for swimming, with a total of 11. He set 26 world records in his 6-year career.[1]

George H. "Babe" Ruth holds many records, including highest career slugging average (.690) and highest average for a World Series (.625 in 1928).[1]

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Glaxo/ ROCHE

Please see reference and Brief Summary of Prescribing Information on next page.

Reference: 1. Russell A, McWhirter N (eds): 1988 *Guinness Book of World Records*, ed 26. New York, Sterling Publishing Co, 1987

Zantac 150 ranitidine HCl/Glaxo 150 mg tablets

Zantac 300 ranitidine HCl/Glaxo 300 mg tablets

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION. Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Glaxo Pharmaceuticals™

May 1988

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ZAN515 Printed in USA August 1988

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

December 3-4—**Annual Meeting of the Arizona Chapter of the American College of Surgeons.** Rancho de los Caballeros, Wickenburg. Sat-Sun. Contact: Lee Ansel, MD, Program Chairman, (602) 251-3131.

January 13-14—**Geriatrics in a Changing Society.** Scottsdale. Fri-Sat. Contact: Jean Kiernat, Institute of Gerontology, (602) 239-5844.

January 27-28—**Coronary Heart Disease Update.** Embassy Suites Hotel, Scottsdale. Fri-Sat. Contact: Deborah Wilderson, Medical Education Resources, 1 (800) 421-3756.

January 27-29—**Mammography and the Search for Breast Cancer.** Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Tess Wade, Breast Clinic of Rochester, (716) 442-8969.

February 10-15—**Laser and Stent Therapy in Vascular Disease: International Congress II.** The Phoenician Resort, Scottsdale. Fri-Wed. Contact: Becky Bowman, Congress Coordinator, (602) 955-1000.

February 22-24—**12th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Phoenix OB/GYN Society, (602) 266-6321.

February 24-25—**Case Studies in ECG Interpretation and Arrhythmia Management.** Clarion Inn at McCormick Ranch, Scottsdale. Fri-Sat. Contact: Medical Education Collaborative, (303) 989-9802.

February 24-26—**Arizona Academy of Family Physicians Annual Scientific Assembly.** Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Shay Southwick, AzAFP, (602) 249-2021.

February 28-March 3—**Pediatric Update 1989.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Barbara Bengtson, Phoenix Children's Hospital, (602) 239-4350.

March 4-8—**Third Annual Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, Barrow Neurological Institute, (602) 285-3956.

March 9-11—**Current Management of Central Nervous System Tumors.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, (602) 285-3178 or 1-800-BARROW-1.

March 30-April 1—**25th Annual Arizona Chest Symposium.** Westin LaPaloma, Tucson. Thurs-Sat. Contact: Susan Thornton, Tucson Medical Center, (602) 327-5461, ext 5110.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologist at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

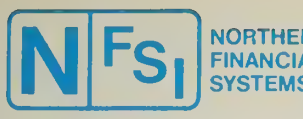
UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 782)



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Indications and Usage: Hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone; in patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

'Dyazide' may be used alone or as an adjunct to other antihypertensive drugs; dosage adjustments may be necessary.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride; potassium supplements (except in presence of severe hypokalemia); anuria, acute and chronic renal insufficiencies or significant renal impairment; hypersensitivity to drug or other sulfonamide-derived drugs; preexisting elevated serum potassium concentration.

Warnings: Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including 'Dyazide'. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving 'Dyazide', when dosages are changed or with any illness that may influence renal function.

If hyperkalemia is suspected, obtain an ECG and monitor serum potassium. If hyperkalemia develops, discontinue 'Dyazide' and initiate thiazide therapy if needed. Persistent hyperkalemia may require dialysis. Monitor serum electrolytes frequently in patients with mild renal dysfunction and in diabetic patients. In patients who may develop respiratory or metabolic acidosis, monitor serum electrolytes and acid/base balance frequently.

Precautions: The bioavailability of the hydrochlorothiazide and triamterene components of 'Dyazide' is about 50% of the maximum obtainable with oral therapy. Theoretically, a patient transferred from therapy with hydrochlorothiazide with or without triamterene might show an increase in blood pressure, fluid retention, or change in serum potassium. Extensive clinical experience with 'Dyazide', however, suggests that these conditions have not been commonly observed in clinical practice. (See CLINICAL PHARMACOLOGY.) Use thiazides cautiously in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease; potassium depletion induced by the thiazide may be important in this connection; administer 'Dyazide' cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases, discontinue 'Dyazide' for a few days; attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion. If patients develop hypokalemia, which is uncommon with 'Dyazide', increase potassium intake (i.e., with supplements or potassium-rich foods). If repeat determinations show serum potassium concentrations below 3.0 mEq/L, discontinue 'Dyazide' and initiate potassium chloride supplementation. Institute corrective measures cautiously and monitor serum potassium concentrations frequently, especially in patients receiving digitalis or those with a history of cardiac arrhythmias. Diuretics may aggravate existing electrolyte imbalances, especially at high dosages or in patients on salt-restricted diets. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Chloride replacement may be required in the treatment of metabolic acidosis. If dilutional hyponatremia develops, restrict water intake. In actual salt depletion, initiate sodium chloride replacement. Use 'Dyazide' cautiously in patients with a history of renal stone formation.

If hyperkalemia develops when treating for hypokalemia, take corrective measures. Also discontinue 'Dyazide' and, if appropriate, substitute a thiazide diuretic until potassium levels return to normal. Do periodic BUN and serum creatinine determinations, especially in the elderly and in patients with suspected or confirmed renal insufficiency. Serum PBI levels may decrease without signs of thyroid disturbance. Discontinue thiazides before conducting parathyroid function tests.

Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine; therefore use cautiously in patients undergoing surgery. Monitor electrolytes in patients taking amphotericin B, corticosteroids or corticotropin concomitantly. Thiazides may potentiate the action of other antihypertensive drugs. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be needed. 'Dyazide' may raise the level of blood uric acid; dosage adjustments of antigout medication may be needed to control hyperuricemia and gout. The following agents given with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq of potassium per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium), and salt substitutes (most contain substantial amounts of potassium). Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium concentrations by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake. Chronic or overuse of laxatives may reduce serum potassium concentrations by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene. The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine. 'Dyazide' will interfere with the fluorescent measurement of quinidine.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Thiazides and triamterene cross the placental barrier and appear in cord blood. The use of thiazides in pregnancy requires weighing the anticipated benefit against possible hazards, including fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Thiazides appear, and triamterene may appear, in breast milk. If use of the drug is essential, the patient should stop nursing. Safety and effectiveness in children have not been established.

Adverse Reactions: The serious adverse effects associated with 'Dyazide' have commonly occurred in less than 0.1% of patients treated with this product. Anaphylaxis, rash, urticaria, photosensitivity, cardiac arrhythmias, postural hypotension, diabetes mellitus, hyperkalemia, hypergiycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia, jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain, acute renal failure, interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment, leukopenia, thrombocytopenia and purpura, megaloblastic anemia, muscle cramps, weakness, fatigue, dizziness, headache, dry mouth, impotence, sialadenitis. Thiazides alone have been shown to cause the following additional adverse reactions: paresthesias, vertigo, xanthopsia, transient blurred vision, allergic pneumonitis, pulmonary edema, respiratory distress, necrotizing vasculitis, exacerbation of lupus, aplastic anemia, agranulocytosis, hemolytic anemia. In neonates and infants: thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.

Supplied: Capsules containing 25 mg. hydrochlorothiazide and 50 mg. triamterene, in bottles of 1000 capsules; in Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

DECEMBER 1988, VOL. XLV, NO. 12

The Chess Game Revisited

Marshall B. Block, M.D.

Almost ten years has elapsed since I wrote an editorial stating that, "We are in a chess game in which moves are being made from multiple sides which will result in us being checkmated." It appears that my prediction was not far off base.

"Our" patients are no longer ours. Patients are now controlled by whatever insurance policy or plan their employer shifts them into depending upon cost factors and accessibility. Physicians in addition can no longer truly direct the patients to a specific hospital. Rather, each individual plan's hospital affiliation determines where that patient will be hospitalized. In order to see patients from most of these plans, physicians must sign agreements which set financial reimbursement for their services. These rates are discounted. In addition, a certain percentage of these fees are withheld to be returned only if the plan itself is financially successful. Since most of the time this is not the case, the income derived from seeing patients from these plans usually approaches 60 percent of billed services. Capitated plans seem to be the goal of many in the health care industry, although only a few seem to be financially successful.

Attempts at forcing physicians into larger networks, at first voluntarily, through PPOs and IPAs is now rapidly becoming legislated locally and nationally. For instance, hospital based IPAs and HMOs tend to meld each group of physicians into a plan which ultimately will lead to closed hospital staffs. The inability for physicians to refer patients to facilities in which they have a financial interest will surely force physicians to form larger corporate entities in order to continue to be able to maintain this additional income which offsets the discounted fees they are getting for their services. Volume will be needed to compensate for the above restrictions which no doubt will lead to disgruntled patients. With less time to spend per patient, the care rendered will no doubt diminish. That, coupled with a capitated system which rewards for less, will add fuel to the ever burning fire of medical/legal exposure.

In order to facilitate care in such a setting, our present archaic record keeping system will need to be overhauled and computerized. It will be impossible to take handwritten notes inasmuch as others who will be caring for your patients on a rotating basis will need to have legible data with which to work. The end of the close personal relationship between physician and patient will again foster more turnover, greater disenchantment with the medical field and further urges for additional controls to make certain that quality is being rendered.

We are, thus, being placed in a Catch-22 position where we are going to be blamed for poor quality when in fact we are being herded into such a situation by the powers that be which are presently legislating the change in the health care industry. This, indeed, is an interesting scenario and will protect the politicians and lawyers in the process. They will be insulated from the adverse publicity which will ensue from the development of such a system and all of the blame will be at Medicine's doorstep. Patients will be complaining about the lack of time spent with physicians, the lack of personal attention, the lack of caring and the limited availability of services. Who will they look to for answers? Not us! Rather, they will be looking at their legislators for

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In This Issue

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- Medical Screening
- New Members
- Classified

From Our President

Richard L. Collins, M.D.

It's not news to any of you that there is a rapidly growing threat to the availability of specialty care and to the funding of compensation for Arizona patients injured in medical accidents.

It may be news that a potential solution is on its way through the planning process.

A more efficient, more expedient and less expensive system which will reimburse injured patients more quickly, more consistently and more predictably is not only possible but practical.

We call one such system "C.A.R.E." – the Compensation And Rehabilitation Effort for Arizona patients. A fault-based medical injury compensation plan, C.A.R.E. would incorporate claims review activity to determine whether or not a standard of care was met, a disciplinary arm to deal with truly negligent physicians, and an administrative board to authorize compensation for injured patients.

Compensation would be provided through a fund which could be jointly financed by physicians, hospitals, insurers and general revenue from the state.

It would compensate patients in three categories: (a) those whose injury or death was caused by medical care which does not meet an acceptable medical standard; (b) mothers or children whose permanent brain damage was caused by medical care provided during labor or delivery; and (c) patients whose permanent brain damage was caused by the administration of anesthesia.

Because the C.A.R.E. system is administrative and not adversarial, attorneys would not be required in many cases; therefore, the availability of compensation would be extended to patients who now have legitimate small claims but do not appeal to contingent fee lawyers.

C.A.R.E. will reduce expenses by instituting periodic payments, capped noneconomic awards, mandatory offset of collateral source payments, prescribed legal awards, and a condensed statute of limitations.

Of course, before the C.A.R.E. proposal can be implemented, a state constitutional amendment is necessary.

Such a change will be expensive and will require a great deal of work. But worthwhile things are rarely cheap, and as we all know, the need is great. Entire communities are losing access to high risk medical services because of unaffordable professional liability insurance; the current system of compensating injured patients is being threatened by the trend toward practicing medicine (a) without insurance (going bare) or (b) with cheaper insurance provided by companies without adequate assets or which do not participate in the state's guaranty fund.

The C.A.R.E. amendment, placed on the 1990 general election ballot, would authorize the state legislature to limit damages, institute periodic payments, limit attorney costs, and establish a patient compensation plan administered by a commission.

The C.A.R.E. system will be analyzed during coming months by an unbiased consultant with expertise in the area of actuarial projections to determine how much it will cost society compared with the present civil court system. If, as we believe, the independent evaluation demonstrates that C.A.R.E. will provide appropriate compensation at a more affordable cost to society – and therefore lead to lower premiums for physicians – we will proceed with its development and promotion.

But we cannot do it alone. We need your help, and your financial support. Let's start by collecting signatures from patients (voters) who will back our plan. Be on the lookout for petition forms mailed to you from the Patient C.A.R.E. Task Force.

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HIV Infection

HIV infection is entirely preventable. Physicians can be an effective tool in curbing this epidemic. The plethora of AIDS-education programs has been directed at the epidemiology, diagnosis and treatment of AIDS. More recently, there have been opportunities to learn about the many issues surrounding HIV counseling and testing. This editorial is directed to the larger challenge to us as physicians: that is, the identification in our practices of persons at risk for HIV infection, and the provision of education and lifestyle change counseling to empower our patients to change those behaviors that put them at risk.

If our practices are in any way representative of the general population, at least 10% of the adult men are gay or bisexual. Another several percent will have a history of IV drug use, the percentage dependent upon the socioeconomic, ethnic and gender characteristics of our practices. Still others may have been recipients of blood or blood products in the earlier years of the AIDS epidemic prior to the institution of careful screening of donors and products. Many of the people with these risk factors will have worries about HIV infection or may be considering testing and need pretest counseling. Some will already be immune suppressed, may be candidates for AZT or prophylactic therapies, or may even be presenting with a clinical manifestation of AIDS that would not necessarily be a part of our differential without knowledge of their risk status. Patients are willing to disclose behavior histories to physicians if the physician utilizes appropriate nonjudgemental history-taking skills.

Primary care physicians routinely include mental and emotional health as a part of overall health. We ask about depression, stress, problems with families, money or job. We must also learn to incorporate sexual health into overall health, and routinely ask questions regarding sexual relationships, behaviors and satisfaction, as well as sexually-transmitted diseases. When asking these questions, we must not presume heterosexuality! In order to do this, we must learn a new vocabulary and, at the same time, learn to withhold judgement on the answers we receive. For example, instead of "Are you married?," we might ask, "Are you sexually active?" If yes, provide a wider range of response possibilities by asking, "With men, women or both?" Once we have identified a sexual behavior that might bring with it risk of HIV infection, we must assess the knowledge and fear base of our patients, be prepared to clarify facts regarding transmission, and provide the educational tools to encourage behavior change.

Traditionally, medical professionals erect barriers between themselves and their IV drug-using patients. If we are to facilitate prevention of HIV transmission in these people, we must teach them to identify their personal risks and give them clear information as to how to reduce those risks. We must teach a drug user to avoid sharing needles or how to effectively clean needles, as well as teach condom use to prevent the sexual spread of the infection to at-risk partners.

Thus, AIDS skills for medical practitioner must go beyond the management of *Pneumocystis Carinii* pnemonia or Kaposi's sarcoma. Skills must go beyond thinking of thrush when a patient presents with a sore throat or looking for severe depression when a person finds out he or she is positive for the AIDS antibody. Skills for the primary care physician must include the identification of patients at risk for HIV infection, the provision of factual AIDS transmission information and lifestyle change counseling in order to empower our patients to change those behaviors that put them at risk for HIV infection.

Kay A. Bauman, M.D., MPH
Clinical Associate Professor
Director, AIDS Education Projects

James E. Dalen, M.D., MPH
Vice Provost for Medical Affairs
Dean, College of Medicine

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See how tax-free income adds up for you

A sensible financial plan is one that eliminates taxes on your investment income--rather than just deferring taxes to a future time.

The equivalent yield table below illustrates the benefits of double tax exemption for individuals under 1988 federal tax rates and under current state tax rates. Locate your income tax bracket (after deductions and exemptions) and read across to see the approximate taxable yield needed to match the tax-free return of a **NUVEEN ARIZONA TRUST.**

For example, with joint taxable income of $29,80 to $71,900, you would be in the 32% combined federal and Arizon tax bracket and would need a taxable investment paying 10.66% t equal a tax-free return of 7.25%.

1988 Taxable Equivalent Yield Table for Arizona

Taxable Income (000)		Combined Federal/State Tax Brackets	Tax-Exempt Yield Equivalents								
Single Return	Joint Return		6.25%	6.50%	6.75%	7.00%	7.25%	7.50%	7.75%	8.00%	8.25%
$17.9- 43.2	$29.8- 71.9	32.0%	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13
43.2-100.5	71.9-192.9	36.5	9.84	10.24	10.63	11.02	11.42	11.81	12.20	12.60	12.99
Over $100.5	Over $192.9	32.0	9.19	9.56	9.93	10.29	10.66	11.03	11.40	11.76	12.13

There is no assurance that state tax rates will remain unchanged. When two state brackets fall within a federal bracket, the higher state bracket is combined with the federal bracket. The state tax rates assumed do not take into account possible adjustment of tax brackets based on changes in the Consumer Price Index.
This example and the yields shown in the table are included for illustrative purposes only and are not intended to be indicative of future performance.

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Medical Screening of Arizona Drivers

The Goal of the Medical Review Program, Motor Vehicle Division, Arizona Department of Transportation, is to ensure highway safety by screening all Arizona driver license applicants, and monitoring licensed drivers, for medical conditions which could affect ability to safely perform driving tasks.

Medical conditions which affect driving ability include those which affect **perception, judgment,** and/or **response.**

Vision loss is the major condition in the area of **perception.** Also included is any type of seizure activity or repeated loss of consciousness. Conditions affecting judgment include psychiatric disorders, substance abuse and degenerative nerve disorders. Conditions affecting **response** include physical disabilities such as paralysis, amputated limbs and arthritis.

A library of resource materials and research on medical impairment and driving, as well as medical review procedures of other states, is kept by the Medical Review Program. This is available to health care practitioners throughout the state.

Driver license examiners throughout the state have been trained by the Medical Review Program Manager, a licensed health care professional, in gross medical screening skills. They have also been trained by a registered occupational therapist in performing road tests and in determining restrictions for vehicle adaptive equipment for the physically disabled.

The Department of Transportation is given the authority by law to screen driving for medical impairment. At the time of application or renewal of license, all persons are required to complete the medical questionnaire set forth at the end of this article.

Based on responses to the questionnaire, a small percentage of applicants are required to submit a medical report prior to licensing (or periodically thereafter if their condition is chronic). These decisions are made under the direction of the Medical Review Program Manager.

In addition to being required to respond to the above questionnaire, persons age 60-69 who are eligible for renewal-by-mail must also submit a vision report prior to licensing. (Persons age 70 and over are not eligible for renewal-by-mail.)

Medical reports must be submitted on one of the Department's official forms. These forms have been prepared in conjunction with representatives of the medical community. State law gives health care providers immunity from personal liability in completing the forms. The Motor Vehicle Division is responsible for making the final licensing decision.

Medical licensing standards are recommended to the Division by its Medical Advisory Board. The Board consists of nine physicians: Glyn Caldwell, M.D., Alan J. Cunnien, M.D., Donald L. Damstra, M.D., Gerald P. Ford, M.D., Thomas Henry, M.D., Robert B. Leonard, M.D., Philip Levy, M.D., William R. Schiller, M.D., and Joseph White, M.D., and one occupational therapist, Cynthia Claus, O.T.R.

Three medical licensing standards were adopted as official state rules in 1987 (R17-4-301-320).

The rule on "general provisions" outlines the medical screening process. It also requires drivers to report, within 5 days or as soon as the condition allows, the occurrence of any medical condition which could affect safe driving ability.

Minimum vision requirements are outlined in the rule on "vision standards." Visual acuity, with binocular vision <u>and</u> acuity of only 20/50 or 20/60 (with best correction) can be licensed with a restriction to daytime driving only. Peripheral vision must be 70 degrees in the temporal approach and 35 degrees in the nasal approach in at least one eye. In addition, telescopic lenses are <u>not</u> allowed for driving.

"Neurological episode standards" outline the required control of episodes (incidents or segments of time involving altered consciousness and/or loss of body control) prior to licensing. All persons must be episode-free for a 12-month period of time **unless** the reporting physician indicates the person meets requirements for one of the exceptions to this and at least 30 days have passed since the most recent episode. Exceptions are: those episodes which occur exclusively during sleep, those which are secondary to an isolated incident, and those which occur during an adjustment of medication on the advice of a physician.

The Medical Advisory Board has determined that no driving restrictions are necessary for the deaf or hard-of-hearing. However, it is recommended that these persons have their vehicles equipped with outside rearview mirrors to compensate visually for their deficit.

There are no state laws in Arizona which <u>require</u> physicians to report patients unable to meet the medical licensing standards. From a liability standpoint, however, it is advisable for physicians to counsel patients to report themselves when they clearly do not

Continued from page 1

redress and additional controls will be placed on the system to ameliorate the above problems. Unfortunately, there will be no solution to the problem if a capitated health care system develops in an HMO mode. A dual system of health care will evolve much as it has in the United Kingdom. Things do indeed look bleak on the horizon and it is of little wonder that medical school applicants are declining. It is not, as some would suggest, because established practicing physicians are negatively influencing future physicians. Rather, one only has to read a newspaper or listen to a news broadcast to feel the hostile machinations which are occurring to Medicine.

The pendulum is still swinging and although we continue to hear that we need to become involved in shaping our future, I think the baton has long ago been passed to others, as we are seen as having biased (self-serving?) viewpoints in the arena of health care delivery.

Marshall B. Block, M.D.
Editor

Medical Screening of Arizona Drivers

meet medical licensing standards. Such counseling can then be documented in the patient's clinical records.

Physicians may report patients whose medical condition makes them high risk drivers. The procedure for doing this is to provide the following information in writing to the Motor Vehicle Division: full name, date of birth (or age), a description of the medical condition, name of the reporting person, address and phone number. The driver is then called in for a re-examination.

Several reference books, which provide guidelines for the physician in determining if a medical condition affects driving performance, are available through the AMA: Medical Condition Affecting Drivers (1986), and Guides to the Evaluation of Permanent Impairment (1984).

For further information on the Medical Review Program, call Jane Lange, Program Manager, at 255-7039. Medical Advisory Board meetings are open to the public and a schedule of meetings for 1988 is available upon request.

MEDICAL QUESTIONNAIRE

PLEASE READ CAREFULLY: The following are medical conditions which, if serious enough, could affect your ability to operate a motor vehicle.

* DIFFICULTY SEEING FROM SIDE TO SIDE (WITHOUT TURNING YOUR HEAD)
* AN EYE DISEASE PERMANENTLY AFFECTING YOUR VISION
* THE LOSS OF NORMAL USE OF A HAND, ARM, FOOT OR LEG
* INADEQUATE REFLEXES IN RESPONDING TO SUDDEN CHANGES IN TRAFFIC
* WITHIN THE PAST TWELVE MONTHS, SUDDEN BLACKOUTS, SEIZURES OR LOSS OF BODY CONTROL (WITHOUT WARNING)
* DIFFICULTY MOVING YOUR HEAD FROM SIDE TO SIDE
* DIFFICULTY KEEPING YOUR BALANCE WHILE SITTING
* AN ADDICTION TO OR LACK OF CONTROL IN THE USE OF ALCOHOL OR DRUGS
* AN ONGOING MENTAL HEALTH CONDITION
* A MEDICAL CONDITION WHICH AFFECTS YOUR JUDGMENT

1. Yes ____ No____ Are you currently addicted to narcotic drugs or are you unable to control your use of alcohol?
2. Yes ____ No____ Do you have a guardian appointed to you by a court for being incapacitated?
3. Yes ____ No____ Do you have any physical disabilities or medical conditions, such as listed above, which affect your ability to drive safely?

If you answered **Yes** to any of the above medical questions, please identify the condition and explain how it affects your driving: _____

CERTIFICATION

I have answered all questions on this application to the best of my knowledge. I understand that making a false statement on a driver license application is a crime and may be punishable under one or more of the following statutes: ARS 28-471.5, 28-472, 13-2702, 13-2407, and 39-161.
I understand that I am required to report in writing to the Motor Vehicle Division any of the listed medical conditions which develop or worsen. I understand and agree that any correspondence or notifications from the Motor Vehicle Division shall be mailed to me at the address shown here or to the newest address provided by me. The Motor Vehicle Division must be notified within ten days in writing of any address change.

Subscribed and sworn to before me this date: _____

_____ Notary / MVD Agent

_____ Signature of Applicant

• 40-5122 5/88

New Members

The Arizona Medical Association welcomes the following new members:

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Sierra Vista
University Autonoma de Ciudad Juarez - 1983

COCONINO

George E. Bryan, M.D.
Neurology
710 N. Beaver Street, Flagstaff
Baylor College of Medicine - 1976

GILA

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Family Practice
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Suite C-1, Phoenix
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Maxillofacial Surgery
P.O. Box 5099, Dept. of
Plastic Surgery, Phoenix
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Faculty of Medicine of the
University of Havana - 1950
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Obstetrics & Gynecology
485 S. Dobson Road
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Autonoma of Guadalajara - 1981
Philip A. Marino, Jr., M.D.
Diagnostic Radiology
5322 W. Northern Avenue,
Glendale
Duke University School of
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Pathology
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Medicine - 1969
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Internal Medicine
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University of Kansas
School of Medicine - 1988

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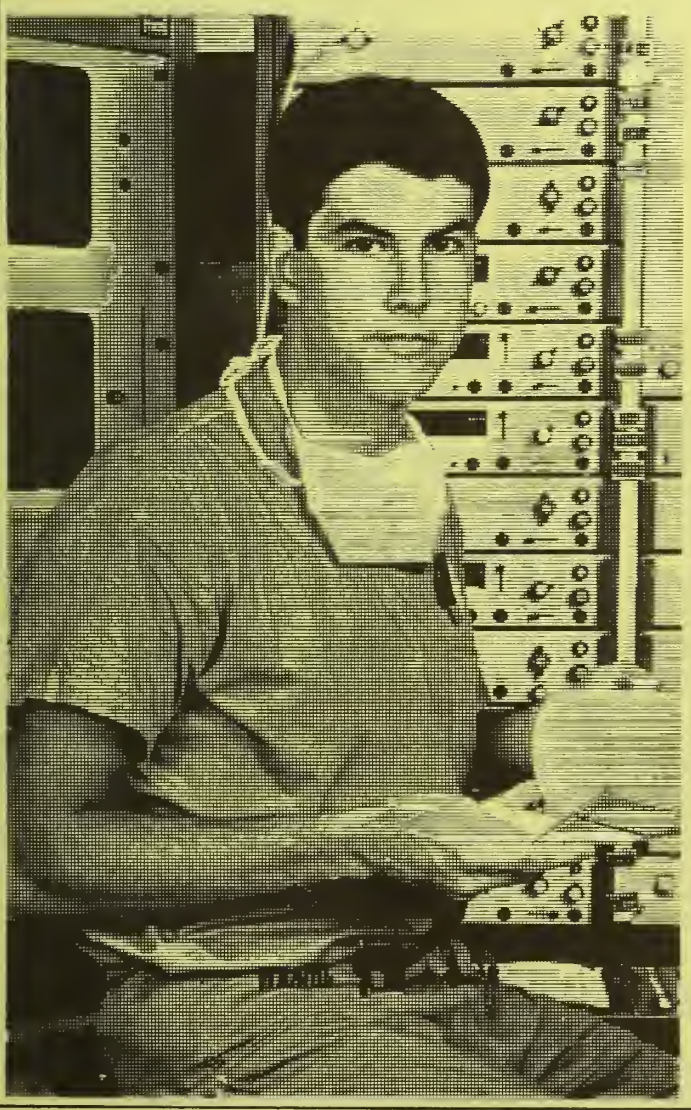

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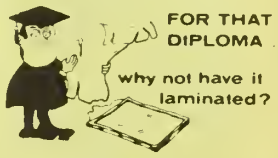

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Women and Medicine

It has become traditional that each December *The Western Journal of Medicine* appears as a special issue. This is the 10th consecutive year that the editors have tried to select a topic that seemed likely to be of increasing importance in medical practice in the years immediately ahead. The topics, in the order of their appearance, have been clinical nutrition, cost of care, geriatrics, occupational and environmental medicine, cross-cultural medicine, personal health maintenance, high tech medicine, medical informatics, AIDS from a global perspective, and, now, women and medicine. For each of these special issues we have been fortunate to find a Special Editor, interested in and knowledgeable of the topic, who was willing and able to take on the formidable task of assembling a special issue of this journal. This year has been no exception. Linda Hawes Clever, MD,* has brought this issue together under the rubric of women and medicine, and it addresses some very important trends and changes that have begun to occur in medical practice and in the medical profession.

There is much new that is happening in both medicine and in our society. Much of it pertains to the sexes. It is no longer the man's world that it was not so very long ago. For much of history the talents of women have too often been submerged, but we now seem to be clearly on the verge of a new era. Women are moving more and more out of the home and into business, industry, and the professions. They are demanding and beginning to receive equal recognition and equal pay for what they do. They have been officially designated a minority for purposes of affirmative action for their employment in both the public and private sectors of society. It is not surprising that all this has been reflected in new attitudes, new insights, and some changes in patient care and within the medical profession itself. There is a new interest in diseases peculiar to women and fresh approaches to understanding and treating them. Paternalism in physician attitudes has given way to greater recognition of women's sensitivities and rights to share more actively in decisions about their care. Women are entering the medical profession in unprecedented numbers, and this surge of women physicians, whether in academia or in practice, is beginning to find expression, and soon will surely have great impact. There is already significant affirmative action to bring more women physicians to positions of leadership in both academia and organized medicine.

This advent of women to status equal with men in our profession and in patient care itself is long overdue. The purpose of this issue will have been served if it provides some insights into what is occurring and if it gives a glimpse of what is certain to be a new and even more exciting era for American medicine in what is the easily foreseeable future. Our thanks to Linda Clever for giving so much of her talents and of herself to the preparation of this very special issue.

MSMW

*Linda Hawes Clever, MD, is a Clinical Professor of Medicine at the University of California, San Francisco, and chairs the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco. She is Chairman Elect of the Board of Governors of the American College of Physicians, as well as Governor of the Northern California region of the American College of Physicians. She is a member of the Institute of Medicine of the National Academy of Sciences and of the Regional Selection Panel for the White House Fellows program. She is a trustee of Stanford University and Immediate Past Chairman of the Board of San Francisco University High School. She is also a wife and mother.

The Guest Editor Speaks

How can *The Western Journal of Medicine* make a difference? By publishing scientifically valid papers. By being readable. By being willing to take some chances. By being creative. By covering diverse topics that appeal to its diverse readership. By stimulating thought and debate. We have tried to achieve all of these goals with this special issue, *Women and Medicine.* We opined that the topic of women *in* medicine has been covered well elsewhere, on the whole. But the topic *Women and Medicine* offered substantial opportunities to explore areas such as diagnosis, treatment, public policy, empathy, kindness, attitudes, and personal and professional values.

This guest editorship has been both challenging and refreshing. My first step after saying yes to Mal Watts' and Holly Smith's invitation was to find topics that physicians wanted to have covered in the special issue. This required interviews, queries at departmental meetings, and assembling a talented advisory group with members Margaret Kaufman; Michel Mandel, MD; Alan Margolis, MD; Sherri Matteo, PhD; Lois Scully, MD; Susan Wall, MD; Ruth Waters; Jennifer Wear, MD; Malcolm Watts, MD; David Werdegar, MD; Dwight Wilbur, MD; Philip Ziring, MD; and medical students Carrie Griffin and Susan Fernyak.

Five general themes were selected: (1) controversial or neglected women's medical problems; (2) the interactions of women, society, and health care; (3) women in medicine; (4) epitomes about common, vexing, recurrent diagnostic and treatment dilemmas; and (5) "testimonials" from women physicians who have managed their complicated lives successfully. The tone was to be constructive and positive, yet provocative.

Once topics were selected, well-informed, thoughtful, articulate authors were recruited with remarkable ease. We could not include some requested topics simply because of space limitations. Along the way it became clear that our goals would be best met not only by publishing articles, but by presenting art, poetry, and quotations that nourish the soul as well as the mind.

An editor does not accomplish but, rather, influences. A guest editor influences only with splendid help. This help came from a number of sources, and I am very grateful to them all. It has been an enormous privilege and pleasure to be the guest editor of this special issue. We hope it makes a difference.

LINDA HAWES CLEVER, MD
Special Issue Editor
Chair, Department of Occupational Health
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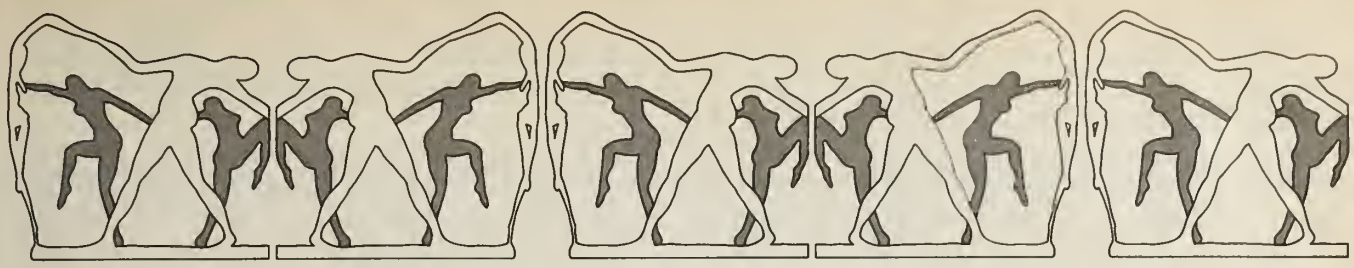

Women and Medicine
From Tension to Truce

The relationship between American women and American physicians has been unsettled for many years, partly because neither side has ever successfully understood the other. A watershed period began, however, with the resurgent women's rights movement of the 1960s and 1970s. The landmark event was the 1973 publication of *Our Bodies, Ourselves,* by the Boston Women's Health Book Collective. The book was the product, in part, of distrust, as stated in its preface:

> We had all experienced similar feelings of frustration and anger toward specific doctors and the medical maze in general, and initially we wanted to do something about those doctors who were condescending, paternalistic, judgmental, and non-informative. . . . We have been asked why this is exclusively a book about women. . . . Our answer is that we are women, and, as women, do not consider ourselves expert on men (as men through the centuries have presumed to be experts on us).[1]

The book was a best-seller.

Today, although feminist suspicion is still with us, women and medicine are beginning to see each other in a different light. This change has many roots, including the legitimation over time of many aspects of the women's movement, growing physician sensitivity to patients as consumers, expansion of the scope of patients' rights, increasing pressure on health care providers to satisfy and thus retain patients, and especially the demographic profile of health care itself.

In 1919, when Alice Hamilton, MD, became the first woman member of the Harvard Medical School faculty, she was prohibited from participating in academic processions and denied faculty football tickets. In 1949 and 1950, only 11% of graduates of American medical schools were women.[2] In 1968, for every woman college student who wanted to be a physician, more than three wanted to be nurses.[3] By 1970, 7% of active physicians were women—the percentage had actually gone down over the course of the century! And, needless to say, the preface of *Our Bodies, Ourselves* virtually assumed that all physicians were men, even as late as 1973.

Today, 37% of first-year medical students are women, as are 15% of active physicians; by 2010, it is estimated that 29% of active physicians will be women. Women comprise 51% of first-year residents in obstetrics and gynecology. For every 8 college women who want to be nurses, 10 want to be physicians. Of nurses, 96% are women, as are 80% of the health care work force. More than half the graduates of master's degree programs in health administration are women.[4]

Furthermore, 60% of patients are women, as are 80% of nursing home patients and 90% of nursing home patients over 85. Of the 25 most common operative procedures, 11 are done exclusively on women. Cesarean section ranks first, hysterectomy third, and repair of current obstetric laceration seventh.[5] And as the US population ages, the predominance of women in the patient population will increase. We are witnessing the feminization of health care, and it promises a new era in the relationship of women and medicine—an era likely to be characterized more by truce than by tension.

This increasingly feminized patient population will be cared for by an increasingly feminized provider population. As we enter a time in which the usefulness, risks, benefits, and costs of care are judged through use of data and quantitative analysis, health care for women will be the subject of disproportionate scrutiny. It is to be hoped that objective standards of appropriate care will replace the acrimonious and often emotional battles of the past over procedures such as mastectomy and cesarean section.

Health care providers are rapidly changing their traditional stances regarding patient autonomy, decision making in death and dying, and patient-physician collaboration. Despite—or perhaps because of—the omnipresent storm cloud of malpractice litigation, both sides are seeking new ways to communicate, to settle differences, to forge relationships based on trust.

In the end, patients want to trust physicians, and with the times so ripe with opportunity, there are good prospects for a negotiated peace. This process will be aided by the fact that more and more physicians are men

and women who have grown up in a more "feminist" era. Changing attitudes and demographics should allow a sorting out of what are gender conflicts and what are patient-physician conflicts; although both merit attention, they involve different issues.

There are other incentives. The patient with the greatest need for health services in the future will be an elderly woman with chronic conditions. Because of physician oversupply in some areas, many practitioners will cater to women patients more than ever. Also, physicians are proving to be quick studies in the face of new ideas and attitudes. Women who now resent the traditional paternalistic attitude of physicians should remember that for centuries, this was the attitude preferred—indeed, demanded—by patients. That physicians are unlearning this behavior in favor of a more interactive relationship is cause for celebration and congratulations.

Certainly, serious problems remain. In too many places, it is difficult, if not impossible, for low-income pregnant women to obtain prenatal services from private obstetricians, producing an open invitation to low birth weight, distressed newborns, and infant and maternal mortality. Women are more likely to be poor and uninsured than are men, and the tragic health problems bred by poverty disproportionately affect them and their children. The explosion in specialty "boutique" health services catering to women raises the spectre of marginal or unnecessary care being provided solely because patients will pay for it. Indeed, in the case of cesarean section, there is widespread agreement that the procedure is used far more often than needed, yet the rate of cesarean deliveries continues to rise.

We have miles to go before true respect between women patients and their care givers becomes the order of the day. This was brought home in 1987 by the tragic case of Angie Carder, who was forced to undergo a cesarean section while she was dying of cancer because male judges and attorneys decided her fetus—which was nonviable—was more important than she was. The operation contributed to Mrs Carder's death. It is probable, however, that when such conflicts arise in the future, more and more physicians will side with their women patients.

The dark days of blind paternalism, distrust, confusion, misconception, and prejudice are fading as patients and physicians grasp for mutual understanding. As lines of communication open, the future is likely to be a time of growing partnership between women and physicians, who are, after all, natural allies. The good news is that they are finally beginning to act like it.

EMILY FRIEDMAN
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* * *

One never notices what has been done;
one can only see what remains to be done.

Marie Curie

Liver Disease in Women

Alcohol, Autoimmunity, and Gallstones

SHEILA SHERLOCK, DBE, MD, FACP(Hon), *London*

Some liver diseases, such as autoimmune liver disease, affect women far more often than men. Others, such as alcohol-related liver disease, progress more rapidly in women than in men. An increased index of suspicion will lead to improved diagnosis and earlier treatment of women with liver disease.

(Sherlock S: Liver disease in women—Alcohol, autoimmunity, and gallstones, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:683-686)

All the common liver diseases in one way or another affect both sexes.[1] Some conditions, however, have not only a somewhat different impact in women but also an increased prevalence.

Alcoholic Liver Disease

In general, the prevalence of alcoholic liver disease is increasing worldwide, particularly in young people and in women. In the United States, cirrhosis is the fourth most common cause of death in white men, and most of it is alcohol-related. There are, however, exceptions to the general increase. In France, alcohol consumption has diminished, reflecting the intense media efforts of the French government. In the United States, between 1974 and 1984, the consumption of commercially produced alcoholic beverages decreased by 0.7% per capita due entirely to a 15.4% decline in the consumption of distilled spirits.[2] The decrease correlated with a fall in cirrhosis mortality. Nevertheless, 52% of respondents to a general survey (63% of the men, 43% of the women) took alcohol within the past year, and 11% of current drinkers (15% of men and 7% of women) reported daily alcohol use. Market research studies in the United Kingdom show that women are drinking twice as much alcohol as a decade ago, with a disproportionate increase in alcohol-related disabilities.[3] The increased alcohol consumption in women can be attributed to a reduction in the cost of alcoholic beverages relevant to earnings, to a ready access to alcohol in supermarkets, and to the reduced social stigmas attached to drinking. A lunch-time martini with friends is now acceptable behavior.

Liver damage due to alcohol use is dose-dependent. It is not related to the type of beverage consumed or its alcohol content. "Safe" daily consumption is uncertain. The limit used to be 160 grams a day, but now 60 grams in men and a mere 20 grams in women, if taken for sufficiently long periods, are known to cause substantial liver damage (Table 1).[4] Steady daily imbibers are much more at risk than "spree" drinkers whose total alcohol intake may be no less. This is partly because intermittent drinkers give their liver a chance to repair and partly because their nutrition status suffers less. Abstaining from alcohol for at least two days each week is recommended for everyone, especially women, and, of course, those who are known to abuse alcohol.

Women present with more severe alcohol-related liver disease than men. Their serum albumin concentrations are lower, prothrombin times are more prolonged, and hepatic histologic changes are more severe.[5] This severe liver disease develops after shorter periods of excess drinking and after consuming lesser amounts of alcohol.[6-8] Brain damage also develops in women after a shorter drinking history and with a lower peak alcohol consumption than in men.[9]

Once liver damage has developed, the progression seems more rapid in women than in men. Thus, alcoholic hepatitis—steatonecrosis, sclerosing hyaline necrosis—the usual precursor of alcoholic cirrhosis, progresses more rapidly in women than in men. This acceleration occurs even if a woman abstains from alcohol.[5] The percentage survival of women with established cirrhosis of alcoholism is reduced compared with that of men (Figure 1).

Various factors must contribute to the increased susceptibility of women to alcoholic liver damage. It is known that women have higher blood ethanol concentrations than men after the same dose even when adjustments are made for body weight.[10] This has been related to changes in ethanol pharmacokinetics during the menstrual cycle,[10] although this hypothesis has not been confirmed.[11] The concentration-time curve after ethanol administration, which measures systemic exposure to orally ingested alcohol, is significantly greater in women than in men.[11] This is probably due to the reduced volume of distribution of alcohol in women compared with men related to their greater proportion of adipose tissue. Thus, although women drink less alcohol per kilogram body weight than men, it persists and is in higher concentrations in the tissues, exposing them to increased toxic effects. There are no major sex differences in the activities of alcohol dehydrogenase—the major alcohol metabolizing enzyme.

Women are less likely to be suspected of alcohol abuse, are more likely to relapse after treatment,[6] and severe pro-

From the Department of Surgery, Royal Free Hospital School of Medicine, University of London.
Reprint requests to Dame Sheila Sherlock, MD, Royal Free Hospital School of Medicine, Pond St, London NW3 2QG, England.

ABBREVIATIONS USED IN TEXT

HLA = human leukocyte antigen
Ig = immunoglobulin

gressive disease is more likely to develop in them. Women should be encouraged to abstain or to consume very little alcohol. Excessive drinkers should be regularly screened with mean corpuscular volume and serum γ-glutamyl transpeptidase estimations, for these tests detect damage and suggest the diagnosis early in the course of alcoholic liver disease.

Autoimmune Chronic Active Hepatitis

Autoimmune chronic active hepatitis is strongly associated with the female sex. This was emphasized in 1956 in one of the earliest articles on the subject from the Rockefeller Institute in New York when it was termed "The Problem of Chronic Liver Disease in Young Women."[12] There are various subdivisions,[13] which are all marked by an 8 to 1 prevalence in women, usually young women or those around the menopause. This female predominance is similar to that of other autoimmune diseases in that humoral immune responsiveness is generally increased in women. There is an association with other autoimmune disorders. Polyclonal gammopathy is usual, and various circulating tissue autoantibodies are found (Table 2). On histologic examination there is a florid picture with pronounced zone 1 lymphocytic and plasma cell infiltration of the parenchyma, liver cells form rosettes, and there is aggressive septum formation and frequently cirrhosis with an absence of significant fat. Patients whose biopsy specimens have these characteristics all show a good response to immunosuppressive (corticosteroid) treatment.

The mechanism of the autoimmune hepatocyte destruction is unknown, but a defect in T-suppressor cells may allow cytotoxicity not only against foreign antigens but against self.[14] The nature of the target antigen on the hepatocyte membrane remains to be determined. Candidate antigens such as liver membrane protein seem to be related to piecemeal necrosis rather than to etiology. Using monoclonal antibodies, attempts are being made to map out the various epitopes contained within the liver membrane antigens so that the immunogenic defect may be studied in more detail. Antibody-dependent cytotoxicity is the main effector mechanism.

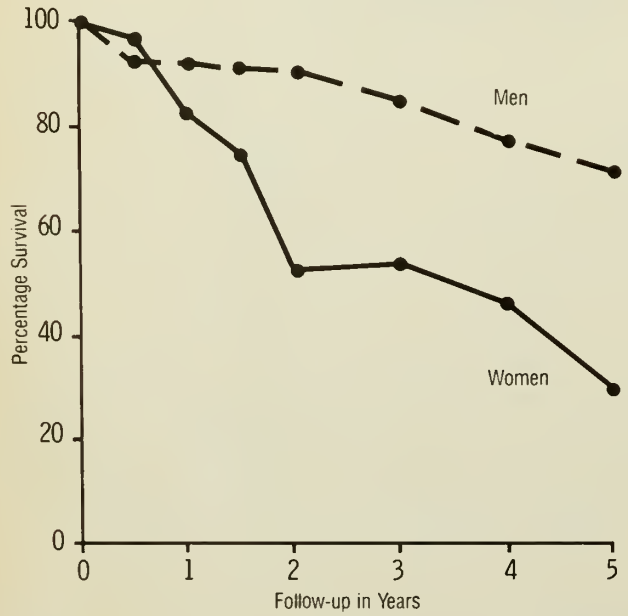

Figure 1.—The graph shows the mortality for alcohol-related cirrhosis in men and women.

TABLE 1.—*Approximate 10-gram Alcohol Equivalents*

Beverage	Alcohol Content Milliliter	Alcohol Content Ounce
Whiskey, gin, and the like	30	1
Wine	100	3
Beer	250	8

Differences between the various types of autoimmune chronic active hepatitis are largely related to different patterns of circulating tissue autoantibodies (Table 2). Overlaps between the subdivisions are found, and further types will undoubtedly be described. Identifying the specific peptide component of the autoantigens responsible will allow more exact classification.

'Lupoid' Type Hepatitis

A type of autoimmune chronic active hepatitis was originally described as "lupoid" because of the presence of lupus erythematosus cells in a small proportion of patients.[14] Affected patients are usually young women, and the general picture is of autoimmune chronic liver disease. Autoantibodies to nuclei are found in a titer greater than 1:160 and to smooth muscle (actin component) in a titer greater than 1:40. The response to corticosteroid therapy is excellent, but a maintenance regimen of 10 to 15 mg prednisolone daily must be continued for many years and in many cases for life, as relapses follow withdrawal. Cirrhosis is not prevented by this treatment.

This type has an association with gene products of the human leukocyte antigens (HLA) of the major histocompatibility complex, particularly class I HLA-B8, with HLA-DR3 as the haplotype; this also applies to other organ-specific autoimmune diseases.[15] This association is found particularly in women younger than 30 years.[16]

Hepatitis Associated With Liver-Kidney-Microsomal Antibody

A second group of autoimmune chronic active hepatitis affects female patients in a ratio of 8 to 1 and is common in children aged 2 to 14 years.[17] It is marked by the presence of serum liver-kidney-microsomal antibodies and a severe course with rapid progression to cirrhosis but with a response to corticosteroid treatment.

Hepatitis Associated With Soluble Liver Antigen

Another type of chronic active hepatitis affects women with a mean age of 35 years.[18] Levels of circulating soluble liver antigen are detected not by conventional immunofluorescence but by radioimmunoassay. Hypergammaglobulinemia is present, and there is a good response to corticosteroid therapy.

Drug-Related Hepatitis

Drug-related chronic active hepatitis affects predominantly middle-aged and elderly women. It has features in common with autoimmune chronic active hepatitis, particularly hypergammaglobulinemia and circulating anti-smooth

TABLE 2.—*Serum Autoantibodies in Immunologic Chronic Active Hepatitis*

Type of Chronic Active Hepatitis	Antibody				
	Smooth Muscle	Nuclear	Soluble Liver Antigen	Liver-Kidney-Microsomal	Mitochondrial
Classic "lupoid"	Yes	Yes	No	No	No
Liver-kidney-microsomal	No	No	No	Yes	No
Soluble liver	Equivocal	No	Yes	No	No
Primary biliary cirrhosis	No	No	No	No	Yes

muscle and antinuclear antibodies. The hepatic histologic features are similar. In the nitrofurantoin-related type, the HLA-B8 genotype may even be present.[19] Other causes include oxyphenisatin—still available in South America—and methyldopa.[20] The chronic hepatitis usually resolves when the responsible drug is identified and withdrawn.

Differential Diagnosis

Chronic viral hepatitis. Until a specific serologic marker of chronic non-A, non-B hepatitis becomes available, possibly within the next year, many patients with autoimmune chronic active hepatitis will be swept into the non-A, non-B "rag bag." They could thus be included in trials of therapy for non-A, non-B hepatitis, for instance with interferon. Caution should be exercised in diagnosing chronic non-A, non-B hepatitis in women unless there is a clear history of an antecedent etiologic factor such as a blood transfusion and the hepatic histologic features are suggestive of non-A, non-B disease.[21(p113)]

A patient's serum should be negative for hepatitis B surface antigen and hepatitis B viral DNA and also lack the immunoglobulin (Ig) M and IgG antibodies against hepatitis B core antigen.

Wilson's disease. Wilson's disease must always be excluded.

Sclerosing cholangitis. Sclerosing cholangitis must be excluded by cholangiography, particularly if there is associated ulcerative colitis, if the serum alkaline phosphatase level is especially high, or if the histologic features of a liver biopsy specimen suggest biliary disease.[21]

Primary Biliary Cirrhosis

In primary biliary cirrhosis, small intrahepatic bile ducts are progressively destroyed and disappear. About 90% of patients are women, usually between the ages of 40 and 59. The disorder is being diagnosed earlier and more often. The combination in a middle-aged woman of chronic pruritus with a raised serum alkaline phosphatase level should arouse suspicion, which is strengthened when an increase in the serum γ-glutamyl transpeptidase concentration confirms that the increased alkaline phosphatase is of biliary origin. A serum antibody against mitochondria is almost always present. A needle liver biopsy specimen may show the diagnostic feature of damaged intralobular ducts surrounded by a dense inflammatory infiltrate rich in plasma cells and histiocytes with granuloma formation. Skilled pathologists can recognize less diagnostic but suggestive changes. If necessary, patency of the major extrahepatic bile ducts can be shown by endoscopic or percutaneous cholangiography.

An awareness of the clinical pattern has allowed primary biliary cirrhosis to be diagnosed much earlier, even before the appearance of jaundice or symptoms. As with other autoimmune diseases, a patient may present with conditions such as rheumatoid arthritis, thyroiditis, or pernicious anemia. A raised serum alkaline phosphatase level is suggestive, and hepatomegaly or hepatosplenomegaly may be presenting clinical signs. The course of these asymptomatic patients is unpredictable: even ten years or more after diagnosis, a patient can remain asymptomatic. Associated conditions include dry eyes and mouth, renal tubular acidosis, jejunal villous atrophy, bacteriuria, pigment gallstones, and a deficiency in fat-soluble vitamins due to steatorrhea. The disease is one of abnormal immune regulation marked by T-suppressor cell depression with T-cell-mediated cytotoxicity to HLA class II antigens on the bile duct epithelium. An unknown antigen may also be involved (Figure 2).[22]

Virtually 100% of patients with primary biliary cirrhosis have serologic antibodies against M2, a specific antigen on the inner mitochondrial membrane. A component of this antigen (E2) has been identified as part of the pyruvate dehydrogenase of the mitochondrion.[23] This discovery will facilitate the development of a specific test for primary biliary cirrhosis. E2 could be related to the unknown antigen believed to exist on biliary epithelium (Figure 2), but so far

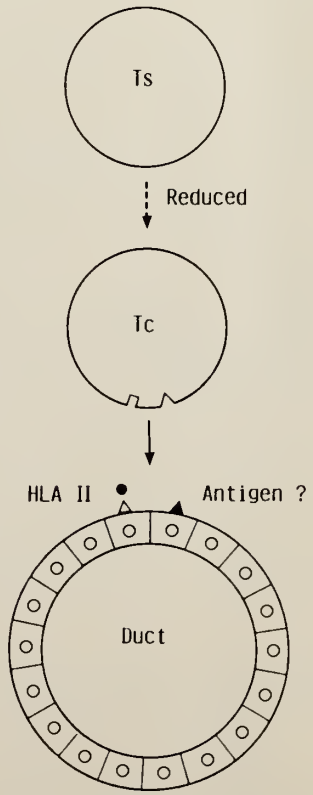

Figure 2.—The diagram shows the possible mechanism of bile duct obstruction in primary biliary cirrhosis. Tc = T-cytotoxic, Ts = T-suppressor cell

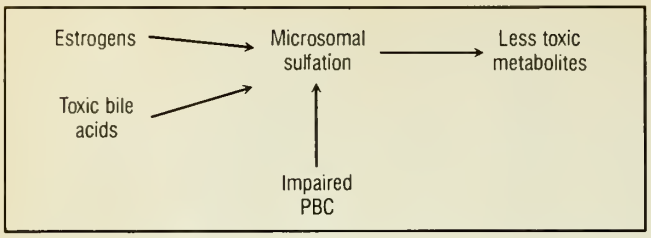

Figure 3.—The diagram shows defective microsomal sulfoxidation in primary biliary cirrhosis (from Olomu et al[24]). PBC = primary biliary cirrhosis

T-cell recognition sites have not been identified within its polypeptide.[23]

Patients with primary biliary cirrhosis have recently been shown to have impaired microsomal sulfation (Figure 3).[24] This is the mechanism by which toxic bile acids and estrogens are detoxicated. This could be related in some way to the predominantly female incidence of this condition.

Although the use of colchicine and cyclosporine has been suggested, no effective treatment has been found, and management is largely symptomatic.[22] Ursodeoxycholic acid is a nontoxic bile acid that competes in hepatocytes with more detergent, toxic ones. It holds promise for improving the results of biochemical tests and lessening the intensity of pruritus.[25]

End-stage primary biliary cirrhosis is one of the most important indications for liver transplantation. The projected five-year posttransplant survival is 66%.[26]

Gallstones

Gallstones are twice as common in women as in men, and this is particularly so before the age of 50. In women younger than 30 years, gallstones are usually associated with pregnancy and obesity.[27]

Estrogens have a mildly cholestatic effect with reduction of hepatic bile acid secretion and the production of more lithogenic bile. The gallbladder empties incompletely in late pregnancy, leaving a large, residual volume that may cause retention of cholesterol crystals. Sludge develops in the gallbladder but usually disappears within a week of delivery.[28] Ultrasonography is particularly useful for diagnosing gallstones during pregnancy.

Bile becomes more lithogenic when women are taking birth control pills. Women taking these over a long term have a twofold increased incidence of gallbladder disease over controls. Postmenopausal women taking estrogen-containing drugs also have a significant increase in gallbladder disease.

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Women and the Acquired Immunodeficiency Syndrome

An Interview

CONSTANCE B. WOFSY, MD, *San Francisco*

SPECIAL EDITOR'S NOTE: *Constance B. Wofsy, MD, is Co-Director of AIDS Activities at San Francisco General Hospital and Medical Center, as well as Associate Clinical Professor of Medicine at the University of California, San Francisco; Assistant Chief, Infectious Diseases, San Francisco General Hospital; and Principal Investigator, Project AWARE (Association for Women's AIDS Research and Education). Although she was not able to contribute an article for WOMEN AND MEDICINE on this very important subject, she kindly agreed to an interview. Both physicians and nonphysicians were asked what questions they had about the acquired immunodeficiency syndrome (AIDS) and the human immunodeficiency virus (HIV) in women.*

(Wofsy CB: Women and the acquired immunodeficiency syndrome—An interview, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:687-690)

WESTERN JOURNAL OF MEDICINE: *Who do you think of when you think of women and AIDS?*

CONSTANCE B. WOFSY, MD: I think of women who are not white, women who have very little control over their lives, and women who are not in a position to ask much of their male partners. I also think of white, middle-class women because the intellectual processing comes from them. They are the women who are going through a lot of self-analysis, who receive the attention in newspapers, and who are talking to one another because they have the verbal skills to discuss the issues. Many of them are disproportionately frightened, while the women who are really at risk are those who have been stigmatized for centuries, who do not think of AIDS as their disease, who are unable to deal with its issues with their male partners, and who have so many other things that are of greater day-to-day risk in their lives. While not irrelevant, something like AIDS, which could happen to them in five to ten years, falls way down on the list of basic issues of survival.

WJM: *What about other women—mothers, for instance—those not necessarily at risk for AIDS?*

DR WOFSY: AIDS is a women's issue, but only a small percentage of women, in fact, are likely to have direct exposure, sexually or by needles. The huge majority of women are involved as mothers, nurses, teachers, social workers, parole officers, counselors, nurturers—the listeners, the teachers of society. When I speak on AIDS, and I do much speaking, the audience is invariably more than 50% women, including at those conferences attended mostly by physicians and the ones dealing with more psychosocial issues. AIDS is a women's disease not only because women are at risk but also as the care givers and the burden bearers.

Mothers of people with AIDS, primarily gay men, are a profound force in this epidemic, and it almost seems that there is a bimodal distribution. At one extreme are the mothers who say, "I want nothing to do with him. He's not my son." At the other extreme are the mothers who go through their own process and become almost politicized, doing things like organizing mothers' support groups. There is another group of mothers who ache for their sons but have to keep it a secret. They may be in retirement in Florida or living in a rural setting. They have come to personal grips with the homosexuality and do everything they can to keep in contact, but they are bearing the burden of the secret along with the son and have no place to unload that burden. They are not rejecting their sons, but they cannot care for them. Another group is mothers who may have cared for a husband who died and now the son is dying. They are older, may not be in good health themselves, and they have a mother's guilt of wanting to provide for her child. These mothers need to be told, "You have to care for yourself as well. Simply because you are a mother, you do not have to become nurse to a dying child. Neither of you will win in that situation." There is that spectrum, from the women who become community activists to mothers who are bearing a silent love and burden to the ones who are really closeted and uncomfortable about the gayness and AIDS.

WJM: *Who is taking care of women with AIDS? No one has them in their private practice. Where are they getting medical care?*

DR WOFSY: There are several answers to that.

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• Most women with AIDS are intravenous (IV) drug users, so the question is not who takes care of women with AIDS but rather, who has IV drug users in their practice. Many of these women are getting care wherever women IV drug users find general medical care.

• Women who are not IV drug users—transfusion recipients, heterosexual women—manage to find whatever physician in their community has gotten some skill and experience treating AIDS. Those physicians with large gay practices have almost invariably not only expressed a willingness but a downright eagerness to diversify and have the experience of treating women with AIDS. Also, women physicians have been willing to take on this care.

• I think the curiosity element is fascinating. The reason physicians are involved with AIDS and interested in seeing women is not just that it is the right thing to do but that it is a different kind of patient, a different kind of problem. Academics look upon women's AIDS issues as a new research opportunity.

The women IV drug users that we see in our research and clinical experiences are very resourceful. Many of them have cleaned up their lives, have gotten their acts together, are off drugs, have remarried, gone through jail sentences, and managed to take care of their children. I am astonished at the resourcefulness of some women who, by sociologic and demographic criteria, would be absolutely at the bottom of the heap. I stand in awe of what they often go through after they find out they are HIV-positive.

WJM: *Are we getting to the women who are most at risk for AIDS?*

Dr Wofsy: It seems to me that women's groups have always focused on whatever active causes there are, and AIDS has become a big issue for many women's groups. There is no lack of interest on the part of women. Getting the information out has become a major cause and mission of women educators in all capacities. Does that get to the IV drug users? It gets to them indirectly, at least, if they come into any place where these women educators are: jails, clinics, prenatal services, planned parenthood groups, and the like.

WJM: *Are there data to suggest that AIDS education efforts are working?*

Dr Wofsy: The information we have is largely about gay men. Gay men who have agreed to be followed prospectively in epidemiologic studies have changed their behavior significantly. These are, by and large, educated, articulate gay men.

In Project AWARE, we have been following both seronegative and seropositive women over time and have found that there is substantial sexual behavior change in a group of women who have agreed to be followed prospectively, with a decreasing incidence of rectal sex, increasing condom use, a decreasing number of partners who are known to be bisexual or homosexual—safer sexual practices. We have had 1 seroconversion in 220 women followed for one year—one seroconversion in seronegative women who have been getting the benefit of our educational efforts and may therefore be a select group. These are just glimpses, and, again, these are women who have the self-interest to participate in a study and to come back over and over again.

WJM: *What is Project AWARE?*

Dr Wofsy: Project AWARE was started in 1985, largely because of an allegation that AIDS was going to spread to the heterosexual population through prostitutes. That seemed to us like an unscientific statement, or at least one that could be tested.

We have studied prostitutes and sexually active women, defining sexually active as five or more partners in the past three years, although we have targeted those with many more partners and sought women on a self-volunteer basis, recruiting in all areas where IV drug use is not expected to be high. We purposely avoided drug treatment centers. Of the women who have volunteered, 5% are seropositive, as are 5% of the approximately 300 prostitutes in our study. Of this entire population, 24% have used drugs, but 46% of the seropositive women were drug users. The strongest association of seropositivity was a personal history of IV drug use or a sustained relationship with a man who was HIV-positive or had AIDS or AIDS-related complex. The women often did not know at the beginning of the relationship that these men were infected.

In the beginning, 1985, we were the first group in San Francisco to study women. In fact, our efforts were dismissed by some because we began our study at a time when there were only five women with AIDS in this city and it was thought that this was just not an issue. Of course, now things have changed and everyone has become fascinated by the subject of women and AIDS.

Another interesting thing is that most of the impetus has come from women. Project AWARE had initially and still has all women investigators. The Women's AIDS Network, a women's information and education organization that is part of the San Francisco AIDS Foundation, is all women, not because men are excluded—they would be welcome—but, again, women taking up the gauntlet and women as motivators are recurring themes in the AIDS issue.

WJM: *Is it true that women with AIDS die faster?*

Dr Wofsy: Neither I nor my colleagues, in all our scanning of the literature, have found documentation that women die faster. In our own experience in San Francisco, the progression of the disease in seropositive women appears to be—this is preliminary analysis—about the same as that in men, but, at the most, these women have been followed for two years. From New York City, there are astonishing data about the decreased survival rates in women. One of the problems when you compare all women with all men is that women are more likely to have opportunistic infections than Kaposi's sarcoma and, thus, their lifespan will be significantly shorter than men's. Men get Kaposi's sarcoma, and Kaposi's sarcoma is always associated with greater longevity in AIDS.

Fischl and colleagues reported decreased survival in a group of women in Florida, but these women had very depressed immune systems on entry into medical care and cannot be readily compared with other study groups.

WJM: *What do we know about the women partners of HIV-positive men?*

Dr Wofsy: There are some curious findings. One of the recurring themes of studies of HIV-positive hemophiliacs is that even here, where the educational base is similar to a cross-section of society, people are not necessarily using safer sex techniques. In Fischl's study from Florida of couples where one was positive and one was negative, about half did not change their sexual practices even when they were in

a study and had access to AIDS education. These people did not practice safer sex techniques even when they got the maximal education, and a prospective study where people are followed every three to six months has got to give as much education as one is going to get.

In our own experience and looking at all studies I know of, it appears that about a quarter of seropositive people choose abstinence from sex, or close to it, as a way of dealing with discordance, whether the woman is positive or the man is, that another 30% to 40% practice some fairly good safer sex techniques, and that another third or more continue with their sexual practices unchanged. These couples have access to education and know the risks. It speaks to the real difficulty of getting to people who consider themselves at only hypothetic risk.

Ironically, it is probably the middle-class, educated person who has taken this thing most seriously, who often is just scared witless, and who has really incorporated safe sex: "I won't sleep with a man who doesn't wear a condom." But very often educated, attractive, articulate women are the ones who get interviewed. The implication is that a woman can have just any man, and she should pick and choose, just like picking a breakfast cereal off the grocery shelf. The fact is, take away 15% of the good looks, add 20% extra weight, and take away a little of the youth, and all of the "no condom, no bed" stuff disappears.

WJM: *Are women who get the virus heterosexually dealing with it any differently than the other AIDS populations you have talked about?*

Dr Wofsy: They often prefer not to be visible about the disease. They usually identify a small number of people with whom they are honest about their illness, and the rest do not know. Unlike gay men, they do not get together in social ways and talk about this issue. Also unlike gay men, who know how to lead organizations and often have access to word processors and newsletters, women with AIDS are too closeted and secretive to spearhead the same kind of internal leadership that could be of help to other women—and I say this without criticism.

Compounding the issue of trying to get word out to the populations at particular risk—blacks and Hispanics, for example—is the implied racism and stereotyping that can be very real but also may be perceived when they were not intended. For black populations, there are a whole bunch of sensitive issues such as the reality of early teen sexuality and pregnancy, the importance of the church yet the avoidance of AIDS issues by church leaders, and the pervasiveness of the drug culture in the inner cities. I am only commenting on those things I have heard black leaders who are very much in touch with the community relate as recurring themes. A black person can say, "The church is not paying attention," but if a white person says, "The black church is not doing anything," that is interpreted as racist.

Another cultural issue involves the counseling of wives of bisexual Latino men. I have learned by listening to leaders in the Latino community and from patients themselves that in the Latino culture, bisexuality is not discussed. A woman does not ask her partner about it, and if he is bisexual and even if she knows, she may think it is none of her business. That is just the way it is. He does his thing and she does hers. It makes counseling difficult. It requires intuitive understanding of important cultural nuances; otherwise, we risk appearing to be judgmental. Many Latino health care workers and others repeatedly stress this important theme.

WJM: *What do you do when a woman discovers her sex partner is HIV-positive?*

Dr Wofsy: Talk, talk, talk. And send her for HIV-antibody testing. Help her deal with her anger and broken trust. Know that time heals. Refer her—and him—to support groups and counselors.

WJM: *What about Pap smears and HIV-positive women?*

Dr Wofsy: HIV-infected women are probably a twofold issue. If there were compliance with the prescribed rate of Pap smears, which, in a high-risk population, would certainly be once a year, we would already be light-years ahead. I do not think there has been a national formulation about whether HIV-infected women should have Pap smears every six months or every year, but if there are repeated episodes of cervicitis or anything abnormal, these women should be referred for colposcopy. There is a strong association of venereal warts with the human papillomavirus, so that if a woman has cervical venereal warts, that mandates a well-taken Pap smear on a yearly basis.

WJM: *What kind of pregnancy counseling are HIV-positive women getting?*

Dr Wofsy: In the population that is most affected, the bearing of children has a very strong role. As a theme, it is really one of the verifications of womanhood. The number of illnesses, ailments, and problems that are being dealt with by these women make AIDS just one more, and a sick baby may not be so big a deal—that is, it is still a baby. Because an HIV-infected woman herself is often well, there may be the hope that if the baby is well, then what they are telling her about her infection is not really true—it is all going to be all right. Unlike an unwanted pregnancy where there is probably a subliminal thought process about abortion before pregnancy occurs, the woman who is pregnant and discovers she is HIV-infected has to make a hard decision very fast and may well just not be able to do so. The general estimates are that less than half of HIV-positive pregnant women decide to abort if they find out they are HIV-positive within the correct time frame.

WJM: *Should all pregnant women be tested?*

Dr Wofsy: I think testing should be offered to all women contemplating pregnancy or already pregnant, so that the issue is discussed. To be realistic, testing should be focused on inner cities and major metropolitan areas. The problem is that physicians elsewhere may deny the problem because it does not appear to be a viable issue, particularly in private practices where there are few women at significant risk. Before any widespread testing is done, however, issues of confidentiality must be worked out.

WJM: *Are you suggesting that testing should be so routine that permission would not be an issue?*

Dr Wofsy: No, I think permission is an issue. I guess by routine I mean that information and the offer of testing with consent should be incorporated into standard care for pregnant women, along with advice about weight and nutrition, testing for syphilis or rubella, and the like.

When one multiplies the cost of the test by the number of

all pregnancies, at this point it may not be cost-effective to be ecumenical. We have to be realistic, as well as all-inclusive. The major metropolitan areas where the prevalence is more than 1% are where the initial programs exist and where the defining of whom to test will take place.

WJM: *If a woman tests positive, what kind of advice should she get?*

Dr Wofsy: If a woman is HIV-positive, she needs neutral abortion counseling. By that I mean that it is her decision. Counseling should proceed along the lines of

Here is what could happen to the child. Here is what life could be like if the child is infected and you decide to carry the child. There is a 30% to 50% chance that the child will be infected and a 50% or more possibility that the child will be normal. If you are infected, there is the possibility that you will become too ill to take care of your child. On the other hand, with advances in science, you might look forward to years and years of a rather healthy life and get real joy out of that child.

Neutral counseling paints the worst picture that could happen and allows an informed decision. People have the right to make informed decisions about other kinds of inherited childhood illnesses and about HIV infection. What they really need to hear—and it needs to be confirmed that they have heard—is what the worst case can be and that the worst case is not just a 1% or 2% chance; it is about 50/50. It has taken me a long time to get to the point where I could give that kind of counseling, and that gets back to the issue of women.

In all likelihood, the majority of counseling will be done by women because they still hold most of the nursing and social services positions, and that means that the women doing the counseling have to be adequately informed. An important thing to remember is that AIDS is so scary that everyone will first look at the information from their own point of view. Everyone will first hear it as it relates to them, and only after they have processed it can they go on and use that information to counsel another person. If a health care worker who has repeated exposure to needles goes to a conference on AIDS, that person will hear only secondarily the general information as it relates to others. First, they will sort out what relates to them. If that person is single and has had more than five sex partners in the past three years, the first thing she will think is, "Am I personally at risk?" Only after that can she process the information to extrapolate it to others for whom she is providing care.

WJM: *Can you imagine any situation where you would not take care of an AIDS patient?*

Dr Wofsy: I have thought about this in relation to airplanes. I do a lot of traveling by air, and I know that a lot of AIDS patients travel, too. I would find it difficult to do mouth-to-mouth resuscitation on an AIDS patient. You can never know what you will do until a situation arises, but CPR [cardiopulmonary resuscitation] is not about saliva, it is about bodily fluids because dying people bite their lips, they bleed, they bite their tongue. If I knew all there was was saliva, I do not think I would have a lot of concern.

This brings up an airline management issue. Airlines should have self-inflating resuscitators (Ambu bags). Mouth-to-mouth is antique. If we can put men on the moon and we can transplant hearts, we can certainly find a way to resuscitate a person without using the mouth. It is absolutely unconscionable not to have resuscitation equipment in a public area where there are episodic cardiac arrests and there is no possibility of getting outside help. The flight attendants are probably trained in cardiopulmonary resuscitation, but they are busy caring for other passengers and always rely on physicians or nurses among the passengers.

WJM: *Do you have any comment on physicians who will not care for AIDS patients or think about not caring for AIDS patients?*

Dr Wofsy: That question breaks down into two parts. The first stage a physician goes through is dealing with the issue of personal risk. That is a real situation, something that everyone has to come to grips with. People need the time to process it, but one cannot have an indefinite amount of time.

The next stage is having the medical competence to care for the kinds of problems that AIDS patients have. A generalist will be more involved in the early care—that is, being able to screen out diarrhea, weight loss, and fatigue as HIV-related versus some other disease. Every generalist has the medical capability to understand the basic issues of the human immunodeficiency virus, and that process has to become part of general primary care.

When it comes to a patient with a complex and multisystem disease, then I have quite a bit of forgiveness for physicians who say, "I don't really feel that I understand all of these infections." If a physician is working where there are going to be a lot of these patients, then that information must be acquired. But in terms of a community where there are episodic cases and there is some multisystem infection, I can well understand that a generalist would say, "This goes beyond me. I will refer this patient for specialized care." I have no quarrel with that whatsoever. On the other hand, when the sixth case of *Pneumocystis* pneumonia comes along in that practice, HIV and associated infections have become part of the routine. That physician has become a budding "AIDS specialist."

WJM: *Any conclusions?*

Dr Wofsy: Women are the heterosexuals who are being infected. Their care is the responsibility of all the men and women who are involved with medical care, ethics, social intervention, and public policy. Women care givers, whether spouses, mothers, or health personnel, need our attention as well.

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A Practical Guide to Preventing Osteoporosis

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Physicians should advise women reaching menopause about the risk of osteoporosis and what practical steps can be taken to reduce this risk. The average woman at menopause can expect to live to be 80 years old; during these years she will face a 15% risk of hip fracture and a 10% risk of vertebral fracture. These risks are increased in Asians and whites, in women who are short and thin, and in those with poorly developed musculature. General advice regarding the correction of certain unhealthy habits and changes in life-style may enhance skeletal health, but prompt restoration and long-term maintenance of physiologic levels of estrogen remain the only proved effective way of reducing bone loss and the risk of fracture.

(Ettinger B: A practical guide to preventing osteoporosis, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:691-695)

Widespread media exposure and intense commercial interest have heightened women's awareness of menopausal health issues. Many women are alarmed by the media's portrayal of osteoporosis as the "hidden epidemic" or the "great crippler." They may hear conflicting advice on the value of various preventive strategies. More than ever before, physicians are being asked to provide sound advice on the prevention of osteoporosis. The purpose of this review is to enhance practicing physicians' ability to provide necessary and practical information about osteoporosis: its etiology, its potential effect on women's health, and what can be done to recognize and reduce the risk of its developing.

What Is Osteoporosis?

Osteoporosis is most easily understood as a reduction in bone mass sufficient to increase the risk of fracture. In a number of ways, osteoporosis is similar to hypertension. Both are common and both are asymptomatic; yet, left untreated, both can increase the risk of the development of serious clinical consequences, such as stroke and hip fracture. Furthermore, both conditions can be diagnosed at an early stage by relatively simple and safe measurements, allowing interventions that will alter the risk of a serious outcome.

Is Osteoporosis Worth Preventing?

Although everyone would agree that strokes are serious and frequent enough to warrant widespread screening for and treatment of hypertension, many physicians and patients do not regard the threat of osteoporotic fracture serious and immediate enough to warrant prophylactic measures. Most articles on osteoporosis quote grim statistics: 1.5 million fractures occur each year among elderly women (including more than 250,000 hip fractures, which have a high morbidity and a 15% mortality); a third of women aged 65 years or older will suffer vertebral and wrist fractures; the annual cost of fracture treatment in the United States is $6 to $8 billion. While these statistics are accurate, they appear to have little influence on physicians' choices to use estrogen, an effective prophylaxis.[1] Many women of menopausal age, when learning of their 15% lifetime risk of hip fracture, may initially be concerned, but they may be reassured by the knowledge that two thirds of these fractures will occur after age 75 years. About a third of hip fracture victims will lose their independence for at least six months, and, for many, the fracture will mark the beginning of a progressive infirmity. Even the wrist fractures caused by osteoporosis may make self-care difficult for elderly women who live alone. Fortunately, wrist fractures heal completely within three to six months and carry no long-term disability. The impact of vertebral deformities is minimal for the vast majority of women. Although a wedge deformity of at least one vertebra may develop in 40% of women, the lifetime risk of a woman suffering a true compression fracture is only about 10%. The best estimates are that only 1 of every 100 vertebral deformities creates sufficient symptoms to require medical attention. Although commonly shown in advertisements, severe thoracic kyphosis, which is caused by multiple vertebral wedges and compressions, is, fortunately, a rare occurrence. In a study of physical and psychosocial consequences of vertebral deformities,[2] we found significant disabilities only in women with more than one severe vertebral deformity. The discomfort and disability of kyphosis are related to the postural change, which causes muscle strain in the lower back. Even in such cases, the back has an excellent capacity to adjust to its new shape, and any disability may be self-limited.

Although osteoporotic fractures create a major drain on our health resources, and although the number of fractures will increase with the "graying of America," one can understand the average menopausal woman's lack of concern. She

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would rather take on an increased risk of fracture in the future than begin a long-term prevention program that requires compliance with possibly inconvenient or bothersome dietary, exercise, and pharmacologic regimens. Some women, however, are at a greatly increased risk of having osteoporosis develop. By identifying these selected women early, a concentrated effort can be made to educate and encourage them to follow recommended preventive strategies.

Achieving Peak Bone Mass

During the years of growth and for several years afterwards, the skeleton accretes mineral. Peak skeletal mass, largely determined by genetic influence, is reached between ages 20 and 30 years. Certain environmental factors may alter peak bone mass; diet and exercise have been under intense investigation. Children growing up in an area of low calcium intake had lower bone mass than those having a high calcium intake because of a ready access to dairy foods.[3] Women 25 to 35 years of age who exercised actively and whose calcium intake—achieved by calcium supplementation—was high had greater skeletal mass than sedentary women whose calcium intake was low.[4] The daily skeletal calcium accretion during peak growth years averages 150 to 200 mg, while the average fractional gastrointestinal absorption of calcium is 25%. For these reasons, the average growing child should ingest at least 800 mg daily. The Recommended Daily Allowance for calcium to meet the needs of the vast majority of children is 1,200 mg. Although calcium deficiency should be avoided at any age, little evidence exists that a high calcium diet has any bone-building effect.

Muscle mass has been shown to correlate closely with bone mass; both are lost concurrently with aging. In healthy young people, strategies for increasing muscle mass have been shown to increase bone mass.[5] Although various exercise regimens may augment bone mass during the period of training, it is not known what portion of the added skeletal mass will be maintained once intensive training has ceased. Other possible strategies for developing high peak bone mass include avoiding smoking and drinking. Pregnancy and using oral contraceptives both appear to correlate with a higher bone mass.

Prevention of Bone Loss

Estrogen Replacement Therapy

Women experience a slow, age-related bone loss after 35 years of age but have accelerated bone loss whenever estrogen deficiency develops. This loss is greatest in trabecular bone but occurs throughout the skeleton. The cause and severity of the estrogen deficiency can modify the rate of bone loss; for example, spinal mineral loss after an oophorectomy is about 50% greater than that seen after spontaneous menopause. Restoring normal estrogen levels is an effective strategy to prevent bone loss in women. Numerous studies have documented the protection provided by estrogen replacement,[6-10] and the dose response of several formulations has been defined. Regardless of the estrogen preparation or the route of administration, a serum estradiol level of 184 to 220 pmol per liter (50 to 60 pg per ml) assures protection. This is the level noted during the follicular phase of the normal menstrual cycle and the level associated with the alleviation of menopausal symptoms. Effective dosages of the commonly used estrogen preparations are conjugated estrogens, 0.625 mg a day[6]; micronized 17β-estradiol, 1.0 mg a day[11]; and transdermal 17β-estradiol, 0.05.[8] In a prospective study, Lindsay and co-workers compared the use of estrogen with that of placebo in women who had had an oophorectomy.[9] Bone mineral levels fell progressively in the placebo group, whereas estrogen use prevented losses. After ten years of study, the structural integrity of the spine was significantly better in estrogen users. A retrospective study of 245 long-term estrogen users yielded additional evidence of estrogen's protection.[10] Compared with carefully matched controls, estrogen users suffered half as many wrist and spine fractures for an average duration of 18 years. Bone mineral content measured at several skeletal sites was significantly greater in estrogen users, varying from 50% greater spinal trabecular mineral to 15% to 20% greater peripheral cortical bone. Recently, technologic advances have allowed the quantitation of bone mass at the hip; a number of reports now confirm that estrogen use has a similar protective effect on bone mass at this site.

It is more difficult to prove that using estrogen prevents hip fractures. Most women suffering hip fractures are older than 75 years, and few women in this age group have used estrogen regularly. Epidemiologists have circumvented this difficulty by applying case-control methods to the relationship of hip fracture and estrogen use. A review of the results of five case-control studies compared estrogen use in 590 patients with hip fracture and 2,021 controls without fracture.[10] The average risk ratio was 0.4, indicating an inverse relationship between estrogen use and hip fracture. A reasonable conclusion is that estrogen protects against fractures of the hip, reducing the risk by half. The incidence of hip fracture in the Framingham cohort was recently reported.[11] The women who used estrogen had a significantly lower risk of fracture, similar to the degree of protection observed in case-control studies. Those who began estrogen therapy at menopause had the greatest degree of protection, but even those who began using estrogen later in life showed some benefit.

The timing and duration of estrogen therapy are important considerations. Even a few years before menopause, women have reduced estradiol levels and bone loss.[12] The spine may suffer a 5% to 10% loss during this transitional period.[13] Most experts agree that estrogen therapy could be initiated in a woman who is at high risk for osteoporosis and who shows signs of dwindling ovarian function (most reliably indicated by irregular menses, vasomotor symptoms, and an elevated level of follicle-stimulating hormone). Is there a time when it is too late to initiate estrogen therapy? Several factors come to bear on this decision. First, most postmenopausal bone loss occurs within ten years following estrogen deprival, after which the rate of bone loss spontaneously slows. Second, estrogen administration merely prevents further loss; it does not rebuild the skeleton. Thus, beginning estrogen therapy for an elderly woman who has lost a third or more of her skeletal mass is less worthwhile than for a recently menopausal woman. Furthermore, evidence suggests that bone loss occurring 15 or more years after menopause has a different cause than that occurring soon after menopause. For this reason, later losses—so-called age-related rather than estrogen-dependent—may be prevented more easily by increasing calcium intake and enhancing its absorption. A regimen of calcium and low-dose vitamin D supplements is more acceptable to patients who are elderly and have never used estrogen.

Finally, women want to know how long to continue taking estrogen. Epidemiologic studies can show a significant reduction in fracture risk in women who have used estrogen more than five years. Because the incidence of hip fracture doubles every five years, there should be a halving in the number of fractures in a population of women who had used estrogen for five years. On the other hand, once estrogen therapy is stopped, a rapid eroding of bone mass can follow. Also, epidemiologic studies have found a trend toward a slightly increased risk of breast cancer in women who have used estrogen for 20 or more years.[14,15] Because of this risk, and because some elderly women find estrogen replacement inconvenient, I usually discontinue or modify it once a woman reaches the age of 65 years. At that time, reasonable alternatives include changing to a lower dosage or administering the estrogen vaginally. Estriol, a much less potent estrogen, is the usual form of estrogen prescribed to elderly women in Europe.

Calcium Supplements

The fear of cancer and concern over estrogen's side effects have prompted many physicians and patients to consider alternative strategies for preventing osteoporosis. Many women believe that a high calcium intake will protect them against osteoporosis. Most studies indicate that high calcium intake has no effect on estrogen-dependent bone loss. After treating postmenopausal women with 1,000 mg of calcium daily for three years, we found that it was totally ineffective in preventing bone loss at several sites.[16] Riis and associates, administering 2,000 mg of calcium, came to a similar conclusion, although some minimal protection of cortical bone was observed.[17] The clear message of a recent international consensus meeting on osteoporosis was that supplementing calcium is not an effective alternative to using estrogen.[18] Despite the lack of benefit from calcium when given alone, adding calcium supplements to suboptimal dosages of estrogen has allowed protection using half the dose (J. C. Gallagher, MD, D. Goldgar, MD, W. T. Kable, MD, unpublished data, November 1988).[7,19] Reducing the dosage of estrogen will reduce the incidence of side effects and will cause less menstrual bleeding, but beneficial effects on menopausal symptoms and lipoproteins will also be minimized.

The usual recommendation for the total daily intake of calcium is 1,000 mg before menopause and 1,500 mg after. Women using standard dosages of estrogen do not require the higher intake. Assessing the adequacy of calcium intake is simple: a diet devoid of dairy products contains about 400 mg of calcium, and each dairy portion contributes about 300 mg. If dietary sources are insufficient to meet a patient's needs, then supplementing with calcium carbonate is appropriate. Oyster shell calcium is cheap and is absorbed well, especially if taken with a meal. Numerous foodstuffs are now supplemented with calcium and could serve as alternative sources.

Exercise

Amenorrheic athletes are subject to bone loss despite intensive training[20]; yet, if their endogenous estrogen production is restored by a reduction in exercise, these athletes may regain bone mass.[21] While a few short-term studies have suggested a beneficial effect of exercise on postmenopausal bone loss, most have failed to show any benefit. In a prospective study, women just after menopause (6 to 36 months) who chose higher levels of physical activity did not have diminished skeletal mineral losses.[19] A cohort of sedentary women eight years postmenopausal on the average was prescribed seven miles of walking each week. During the three years of study, these women showed a 28% increase in energy expenditure but no reduction in skeletal losses.[22] The bone mass of postmenopausal endurance runners, average age 62 years, tended to be lower than that of sedentary women of the same age.[23] In older women, various exercise prescriptions, evaluated for brief intervals, have shown increases in bone mass. Unfortunately, short-term gains induced by vigorous exercise are rapidly lost once the training is discontinued.[24] Notelovitz and co-workers found that an intensive program of muscle conditioning increased the osteotrophic effect of a regimen of 0.625 mg of conjugated estrogens for more than a year (M. Notelovitz, MD, PhD, D. Martin, PhD, R. Tesar, PhD, L. McKenzie, RN, and C. Fields, RN, unpublished data, November 1988). It remains to be proved whether adding exercise, like adding calcium, could augment the osteotrophic effects of suboptimal levels of estrogen.

Other Pharmacologic Agents

Agents that may be effective in reducing the rapid loss of bone in the period immediately after menopause include calcitonin, thiazide diuretics, progestogens, and a combination of cyclically used agents. Christiansen and colleagues in a two-year study found that thiazide therapy appeared to reduce the rate of bone loss slightly, largely because of transient stabilization during the first six months of treatment.[25] Although no long-term prospective studies have been done, one cross-sectional study of hypertensive postmenopausal women showed that bone mass was higher in thiazide users.[26] Women using estrogen had greater bone mass than thiazide users, but women using both agents had the highest bone mass of all. In this study, the prevalence of fractures was inversely related to bone mineral; the prevalence of fractures was halved in women using either thiazides or estrogen and was 84% less in women using both drugs compared with those using neither. In another retrospective study, thiazide users carefully matched to nonusers did not show such benefits.[27] Because thiazide therapy is associated with significant side effects in normotensive persons, widespread use by normotensive postmenopausal women cannot be recommended.

Calcitonin is a polypeptide hormone secreted by the C cells of the thyroid. Human and salmon calcitonin preparations are commercially available and have been widely used for the treatment of Paget's disease. Like estrogen, calcitonin acts to prevent bone loss through a reduction in bone resorption. Calcitonin has not been widely accepted as an alternative to estrogen because of its cost ($2,000 to $3,000 per year) and difficulties in its administration (daily injections). The intranasal administration of calcitonin is being evaluated, and preliminary results are encouraging.[28]

Although some experimental evidence has suggested that progestogens have an intrinsic osteotrophic effect, most clinical trials have shown equivocal or no protection against bone loss. Lindsay and associates found that the use of 19-nor-17β-hydroxyprogesterone protected ten menopausal women against cortical bone loss.[29] This study, because it used few subjects (with only one year of follow-up) and examined a relatively insensitive skeletal site, may have lacked statistical power to show losses. Hart and co-workers studied two other progestogens, norgestrel and norethisterone, finding only the

latter to be effective during a two-year trial.[30] Gallagher and co-workers found that giving medroxyprogesterone acetate, 20 mg daily, did not protect against mineral loss in the spine but may have had a partially protective effect on appendicular cortical bone (J. C. Gallagher, MD, D. Goldgar, MD, and W. T. Kable, MD, unpublished data, November 1988). Our experience with giving medroxyprogesterone acetate, 10 mg daily, substantiates a minimal protective effect on spinal mineral. Unfortunately, 19-nor progestogens and high doses of C-21 progestogens adversely affect high- and low-density lipoprotein cholesterol, making it likely that their long-term use will increase the risk of cardiovascular disease. An adverse effect on mood and energy, similar to the premenstrual syndrome, is commonly observed when these agents are given in large doses, especially without estrogen.

Coherence therapy, first proposed by Frost,[31] involves cyclic treatment with a series of agents. The acronym ADFR stands for the four phases of the regimen: *A*ctivation of osteoclasts, *D*epression of these same cells before their resorption potential is fully realized, a drug-*F*ree period to allow bone to be formed at these activated sites, and *R*epetition of the cycle. The goal of this approach is to tip the balance between bone resorption and formation toward increased formation. This exciting area of skeletal research is still in its primitive stages, but a number of agents and schedules are being evaluated. Patient compliance is good because these agents are administered for only a few days every few months. Preliminary reports of maintenance or increases in trabecular bone volume and bone density have been greeted with enthusiasm, but other reports have failed to show beneficial effects.[32]

Selecting Women at High Risk for Osteoporosis

Certain clinical factors seem highly protective. Being obese, for example, greatly reduces a woman's risk of hip fracture. The Framingham group reported that women who were 25% or more above ideal weight had half the incidence of hip fracture.[11] Blacks and Latinos are much less prone to osteoporosis; Asians have about the same risk as whites. Women who are petite and who have a poorly developed muscle mass are likely to have a poorly developed skeletal mass. Heavy smoking and a heavy intake of alcohol are also associated with an increased risk; smoking reduces the levels of estrogen (both endogenous and exogenous) and is associated with both lower body weight and an earlier menopause; alcohol appears to have a direct toxic effect on bone, as well as increasing the likelihood of falls and injury.

While the quantity of bone mineral accounts for a large part of the risk of fracture, another important factor may be the way in which mechanical forces are applied to the skeleton. For example, women with spinal curvature seem especially prone to vertebral compression fractures, while women with inadequate defenses against falling are at high risk for hip fracture. Life expectancy is one factor that rarely receives consideration in osteoporosis counseling. Age is the most powerful predictor of risk, and prophylactic measures should be greatest in those women whose health and family history enhance their chances of living beyond the age of 80 years. Epidemiologic studies have suggested numerous other risk factors but these, singly or in combination, lack any discriminatory power in individual women.

In discussing osteoporosis with patients, I find it useful to apply the analogy of a "bone bank account"; most "deposits" are made in adolescence and most "withdrawals" are made in the several years after menopause. Ultimately—after 30% to 50% of skeletal mass is lost—will the skeleton become "bankrupt" and unable to meet simple physical demands put on it? Noninvasive bone density measurements developed over the past two decades allow a safe and accurate quantification of bone mass. Bone mass is the best predictor of a subsequent fracture risk.[33] The best predictor of what the bone mass will be at age 75 years is the bone mass at menopause. Measuring the spinal density is preferred over appendicular sites; quantitative computed tomography, dual-photon absorptiometry, or the newly developed dual-energy x-ray absorptiometry can all serve this purpose; each costs about $150 to $250. These tests should be reserved for women who are ambivalent about beginning prophylactic therapy. With wise counseling from physicians, they can consider their chances of osteoporosis developing based on objective data and weigh this risk against the potential risks, cost, and inconveniences of prophylaxis.

Evaluating the risks and benefits of estrogen replacement therapy is beyond the scope of this review. A considerable body of epidemiologic data indicates that the long-term use of postmenopausal estrogen confers a major health benefit by reducing cardiovascular disease. Physicians who intend to prescribe estrogen should become familiar with current recommendations for formulation, dosage, route, schedule, and progestogen cotherapy. Up-to-date comprehensive reviews appear in the May 1987 issue of the *American Journal of Obstetrics and Gynecology*[34] and in the November 1988 supplement to *Obstetrics and Gynecology*.[35] Although it is reasonable to alter habits that could adversely affect bone mass—smoking, drinking alcohol, a sedentary life-style, and low calcium intake—the skeletal benefits of such changes have not been adequately evaluated. Correcting estrogen deficiency remains the best way for menopausal women to reduce their risk of osteoporosis.

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The Last Words of My English Grandmother

There were some dirty plates
and a glass of milk
beside her on a small table
near the rank, disheveled bed—

Wrinkled and nearly blind
she lay and snored
rousing with anger in her tones
to cry for food,

Gimme something to eat—
They're starving me—
I'm all right I won't go
to the hospital. No, no, no

Give me something to eat
Let me take you
to the hospital, I said
and after you are well

you can do as you please.
She smiled, Yes
you do what you please first
then I can do what I please—

Oh, oh, oh! she cried
as the ambulance men lifted
her to the stretcher—
Is this what you call

making me comfortable?
By now her mind was clear—
Oh you think you're smart
you young people,

she said, but I'll tell you
you don't know anything.
Then we started.
On the way

we passed a long row
of elms. She looked at them
awhile out of
the ambulance window and said,

What are all those
fuzzy-looking things out there?
Trees? Well, I'm tired
of them and rolled her head away.

William Carlos Williams

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Women and Medicine

The Health of Adolescent Women in the 1980s

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The opportunities and stresses faced by today's adolescent women have the potential to affect their health, either directly or through interaction with biologic and psychosocial events. Recently achieved entry into the world of endurance and competitive sports; smoking, drug, and alcohol use; the toxic shock syndrome; and the acquired immunodeficiency syndrome threaten the health of young women today. Physicians who care for adolescent women in the 1980s and in the future will require special skills to do so successfully.

(Litt IF: The health of adolescent women in the 1980s, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:696-699)

Along with increasing opportunities and scientific advances geared to improving the health and social well-being of women in the past decade have come new and greater stresses and threats to their health. This is particularly true for adolescent women who must now contend not only with pubertal changes in their bodies but also with changing messages and expectations from the non-consensus society in which they are growing up. For physicians this presents an exciting challenge to preserve health and encourage health-promoting behaviors at this time of rapid physical and psychosocial growth along an uncharted path. To meet this challenge, this article will focus on the special health needs of adolescent girls.

Mortality data for adolescents show that the leading causes of death are automotive accidents, suicides, and homicides.[1] The incidence of death from each of these is considerably higher for male than for female adolescents, with the latter dying in accidents more often as passengers than as drivers and accounting for more suicide attempts than completed suicides.

Morbidity rates are perhaps more indicative of the health problems of adolescent females. First to be considered are those conditions that are directly related to their biology, the process of pubertal development. Puberty effects differences in body habitus between the sexes, in addition to the obvious secondary sex characteristics. A female adolescent increases her percent body fat from the unisex childhood figure of 8% to 22% by the completion of puberty. One potential advantage of increased adiposity in women is the increased buoyancy it produces, giving them an advantage in swimming events.

For the most part, however, the increased weight of puberty, coupled with the change in configuration of the female hip girdle, is viewed negatively by adolescent women of the 1980s.[2] Growing up in a society that values thinness as the idealized female form, adolescent women have been encouraged by the media and peers to diet and engage in unhealthful eating behaviors such as self-induced vomiting,[3] the use of laxatives, and, in some, a resort to anorexia nervosa or bulimia, the reported incidence of which has increased fourfold in the past two decades.[4] A primary care physician may be in a position to ameliorate these all-too-common sequelae by anticipating with a prepubertal child the bodily changes she is soon to experience in a positive light. For an already pubertal young woman, charting her height and weight on standardized growth curves to inject some reality-testing about the normalcy of her weight may prove helpful. If she persists in her desire to diet, providing a healthy weight-reduction regimen can be encouraged through the use of exercise and diet that results in no more than a 0.9-kg (2-lb) loss weekly. An early recognition of complex psychosocial problems followed by prompt expert counseling may prevent more serious eating disorders.

Puberty also results in a wider angle between the femur and the knee that, in combination with laxer ligaments, may predispose to increased injuries to the knees during athletic activity. Proper coaching and footgear should prevent this risk from being realized, however.

Most of the other physical changes of puberty also favor male athletes, who enjoy improved cardiac and pulmonary size and functional capacity, greatly increased musculature and, hence, strength, and an increased number of erythrocytes with resultant increased oxygen-carrying capacity compared with pubertal female athletes. The last effect is compounded by the physiologically determined lower hematocrit resulting from suppressed erythropoietin with increasing levels of estrogens during pubertal development, but also through increased iron losses through menstruation—if not experiencing athletic amenorrhea—through sweat, and through inadequate dietary intake. It is therefore not surprising that a recent study of adolescent cross-country runners found iron deficiency in female and male runners at the start of the season and at its completion.[5] Of great interest in this study was the finding that the majority had normal hematocrits and erythrocyte indices, with iron deficiency diagnosable only by determining ferritin levels. Physicians

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caring for adolescent female athletes should, therefore, determine the hematocrit, as well as ferritin levels, before, during, and after the competitive season; monitor diet to ensure adequate iron intake (18 mg elemental iron daily); and avoid prescribing nonsteroidal inflammatory drugs for minor injuries—if necessary, only with food—to avoid additional stool losses of blood that often result from this practice.

Other nutritional deficiencies that occur commonly among adolescent women who are weight conscious or athletes, or both, include those of calcium and zinc. Because of the image of milk products as being fattening, they are often shunned, and few get the four to six servings that provide the 2 grams of calcium needed to maintain the integrity of pubertal bone. The additional risk of osteoporosis posed by the estrogen deficiency caused by athletic amenorrhea in many of these women must also be recognized and, it is hoped, prevented by supplementing deficient diets. We have found that those who engage in restrictive dieting or rigorous exercise such as gymnastics or ballet dancing before puberty, with resultant pubertal delay, appear to be at particular risk for this complication.[6] Antacid products such as Tums E-X (calcium carbonate, 500 mg a tablet) provide 300 mg of absorbable elemental calcium for each tablet and are therefore convenient to use and less expensive than other supplements.

Zinc deficiency is more difficult to establish but should be suspected in young adolescents who do not get the recommended amount of animal protein in their diets. As cognitive development during adolescence not uncommonly results in idealism, vegetarianism often is espoused for the first time at this stage of life. Vegetarian adolescents can get a healthy, growth-promoting diet but require careful supervision to ensure an adequate intake of usable protein and vitamins.[7] Support from an understanding physician is crucial if this is to be successful.

One of the more obvious consequences of puberty is a change in the configuration, size, and function of reproductive organs. Ovulation and resultant menses or their absence may be problematic for an adolescent and are often responsible for the health problems of this age group.[8] Primary amenorrhea—the failure of menses to occur within two years of secondary sex characteristics or by age 16—may occur because of genetic disorders such as the Turner syndrome; congenital anomalies, such as an imperforate hymen; a central nervous system neoplasm, such as craniopharyngioma; disordered secretion of gonadotropin-releasing hormone by the hypothalamus; or gonadotropins by the pituitary (the polycystic ovary syndrome); chronic illness, such as cyanotic congenital heart disease or inflammatory bowel disease; starvation; stress (emotional or physical); or rigorous exercise. Secondary amenorrhea—the cessation of previously established menses for four or more months—may result from any of these, other than the genetic or congenital causes.

With the recent relaxing of restrictions preventing the involvement of women in competitive athletics has come the recognition of the phenomenon of "athletic amenorrhea."[9] There are a number of hypotheses as to its etiology, including the associated weight loss, low body fat, stress, or self-selection. Since the now controversial studies of Frisch and McArthur, it has been recognized that there is a relationship between body fat and menstrual function.[10] These authors suggested that a person must reach a critical weight of 48 kg (106 lb) or 17% body fat to have menarche and 22% body fat for normal monthly menses thereafter. Obese girls do have menarche earlier than those who are lean, and weight loss of as little as 10% in an obese woman may be sufficient to cause amenorrhea. Studies by Bullen and co-workers in which two groups of college women underwent identical programs of rigorous aerobic training resulted in amenorrhea only in the group that actually lost weight and not in the other, in which weight was experimentally maintained, supporting the weight-loss hypothesis.[11] On the other hand, there are a number of reports of athletes with body fat of less than 10% who menstruate normally and others showing that the menses resumed in athletes forced to rest following injury in whom there is no change in weight or body fat. Pubertal delay and primary amenorrhea in adolescent ballet dancers with body fat as high as 22% to 24% have been reported as well.[12] In this study, a rapid progression of pubertal development followed the forced cessation of training after an injury.

Emotional stress may trigger amenorrhea in adolescents, as seen in the well-recognized "boarding school syndrome" and reports of amenorrhea among concentration camp victims. Accordingly, it has been postulated that the stress of competition may be sufficient to cause athletic amenorrhea. This explanation has been challenged by Warren, who compared the age at menarche of ballet dancers with that of another group imbued with the stress of competition—namely, music students—and found the latter to have menarcheal ages similar to those of controls and considerably earlier than those of the athletes.[12]

The possible role of physical stress in the pathogenesis of athletic amenorrhea has been extensively explored. It has been shown that the incidence of amenorrhea, oligomenorrhea, and luteal phase defects increases with increasing duration and intensity of training. For example, the incidence of amenorrhea in women runners rises exponentially once they have exceeded 20 miles per week.[13] Studies of women under experimentally increasing intensity of physical training have shown increased levels of "stress" and "antireproductive" hormones and neurotransmitters, such as dopamine, endorphins, and norepinephrine.[14] On the other hand, similar levels of physical stress among athletes in sports other than running are not associated with the same incidence of amenorrhea. For example, world-class swimmers and volleyball players have an incidence of menstrual disorders comparable to that of nonathletes. Exploration of this observation to explain athletic amenorrhea is now timely. Malina has suggested that certain types of body habitus are desirable for different sports.[15] Accordingly, girls who are shorter and fatter than average are well suited for swimming, whereas taller, leaner girls with a lower upper-to-lower-body ratio make good sprinters, runners, or ballet dancers. These differences in body habitus are also related to differences in the timing of menarche, such that early maturing girls tend to be shorter and heavier and later maturers taller, leaner, and with a lower upper-to-lower-body ratio. Perhaps, according to Malina, there is self-selection favoring the choice of certain sports by those with different pubertal maturational patterns, rather than the sport causing the pubertal differences.[13]

Regardless of the cause of amenorrhea, physicians caring for adolescent amenorrheic athletes must first rule out causes other than athletics and, once that is done, work with the teenagers to prevent its sequelae. The possibility of hormonal replacement and calcium supplementation should be

carefully considered, particularly in a youngster with amenorrhea of more than a year's duration or one who is more than a year older than were other family members at the time of their menarche. If she is sexually active, oral contraceptives should be recommended to prevent both osteoporosis and pregnancy. In our experience, sexually active athletes—as well as patients with anorexia nervosa—who have amenorrhea typically decrease their pregnancy vigilance, occasionally with surprising and unfortunate outcomes. There are a few data to support the recommendation that competitive adolescent athletes with amenorrhea take the summer off from all athletics, after which menses may return. Alternatively, the menses have been restored by decreasing the frequency and intensity of training by 10%.[9]

Another common gynecologic problem of adolescent women is dysmenorrhea, the leading cause of short-term school absence among girls. A third of adolescent women suffer from incapacitating dysmenorrhea, yet they rarely seek help from physicians for this condition, perhaps having been conditioned by their mothers to "grin and bear it." Happily, in the 1980s this is no longer necessary, as the pathogenesis of dysmenorrhea is now known and its prevention possible. Because it is caused by increased levels of prostaglandins $E_2$and $F_{2\alpha}$ in the endometrium, administering prostaglandin inhibitors, such as naproxen sodium—550 mg with the onset of the period and 275 mg every six hours thereafter for one to two days—is usually effective in preventing cramps. Alternatively, if the teenager is sexually active, ovulation can be inhibited, resulting in an alleviation of cramps, with a combination oral contraceptive. Failure of these approaches to prevent or treat dysmenorrhea is an indication for laparoscopy to explore the possibility that the pain is due to endometriosis, now recognized to begin during adolescence and often difficult to diagnose on the basis of a pelvic examination alone.[8]

The differential diagnosis, and hence the management of menometrorrhagia in adolescents, differs somewhat from that in older women. Possibilities to be considered include von Willebrand's disease when there is massive bleeding with the first menstrual period; a surreptitious misuse of oral contraceptives; and trauma or pregnancy that an embarrassed adolescent may be reluctant to reveal unless sensitively interviewed. The most common cause of excessive menstrual bleeding during the first postmenarcheal year, however, is anovulatory cycles. Unlike the management of older patients with heavy bleeding, a dilatation and curettage procedure rarely needs to be done in an adolescent with heavy bleeding as there is almost no risk for endometrial cancer. A tapering oral regimen of high-dose estrogen and progestin combinations or administering medroxyprogesterone acetate (Provera) is usually therapeutic.[8]

The selection of a contraceptive method with a sexually active adolescent must take into account the special biologic and psychosocial issues of this age group.[16] Biologic considerations include the following:

- A high incidence of dysmenorrhea that favors the use of ovulation-inhibiting oral contraceptives and argues against the use of an intrauterine device.
- The stage of pubertal growth may cause concern about administering estrogens to a youngster who has not yet completed her growth spurt. This is usually not an important consideration, as most girls have had menarche before becoming sexually active and are likely to have completed the growth spurt by that time. Moreover, the small amount of estrogen in oral contraceptive pills is unlikely to be adequate to inhibit growth.
- There is an increased risk of "post-pill amenorrhea" in those who had irregular menses or anovulatory cycles before using estrogen-containing oral contraceptives, and young teenagers should be informed of this possibility.
- The histologic characteristics of the early pubertal cervix, being largely composed of columnar epithelium, make it more susceptible to infection, contributing to the increased risk of contracting a sexually transmitted disease. The risk of infection with the human immunodeficiency virus (HIV), pelvic inflammatory disease, and other sexually transmitted diseases is substantial in this age group. The use of a condom and spermicidal foam provides excellent protection against these diseases—particularly HIV infection—and should be considered when both partners are motivated. Because of this increased susceptibility to sexually transmitted diseases—particularly salpingitis, with the risk of infertility as a result—the use of an intrauterine device should be discouraged.
- The high risk of the toxic shock syndrome in adolescents makes the use of any object that remains in the vagina for more than a few hours, such as a superabsorbent tampon, contraceptive sponge, or diaphragm, potentially dangerous.
- The serious medical consequences of pregnancy in those younger than 15 years remind us of the importance of using the most effective contraceptive method available and weighing its potential side effects against the possibly fatal complications of pregnancy itself in this age group.

The following psychosocial issues need to be assessed in choosing a contraceptive method with a teenager:

- Self-esteem, as it has been shown that poor self-esteem is associated with poor contraceptive compliance. Such a patient is probably a better candidate for a passive contraceptive method, such as an intrauterine device (generally contraindicated because of risk of infection), medroxyprogesterone (once this is again released for use), or close follow-up if another method is chosen.
- A need for confidentiality—that is, if a teenager is afraid of discovery of her contraceptive method by her parent(s), she is likely not to use it.
- Immature communication skills may make it difficult for an adolescent to discuss the need for protection with her boyfriend and may also limit her access to a health care facility to get contraception.
- Feeling invulnerable is common in this age group. This may lead a teenager to feel not at risk for pregnancy. Discussing reproductive physiology in a way that relates to the patient herself, such as by having her keep a basal body temperature chart to show when she is ovulating, may be useful.

Having just discussed care of sexually active adolescent girls, it is appropriate to expand the discussion to include those whose sexual activity is with a member of the same sex. Adolescent lesbians often need support in clarifying their sexual preference, protection against pregnancy or sexually transmitted diseases when trying to deny their sexual orientation, and assistance in dealing with their families.

Advances in equality between the sexes have had one

unfortunate consequence. Whereas previously the number of male adolescents who used drugs and alcohol and smoked far exceeded that of adolescent girls, the gap has rapidly narrowed. For example, 13.6% of female adolescents now smoke, compared with 13.1% of male adolescents.[17] The health-destroying effects are both immediate—a higher incidence of respiratory tract infections and decreased vital capacity—and long-range. For the first time in history, in 1985 the death rate from lung cancer exceeded that from breast cancer in women in eight states. Moreover, the reported antiestrogenic effects of smoking may result in an increased incidence of osteoporosis and, potentially, reproductive dysfunction in later life.[18]

The sex differences in metabolizing drugs and alcohol have only recently been recognized. For example, the effect of estrogen is to delay the metabolism of alcohol, with the end result that the same amount of alcohol produces a higher blood alcohol level in women than in male counterparts. There are also differences that relate to estrogen levels at different phases of the menstrual cycle and the use of estrogen-containing oral contraceptives. The puberty-related increase in adiposity also contributes to storage and release of fat-soluble substances. As a result of these phenomena, mostly unknown to adolescent women, they are at greater risk for toxicity, accidents, and legal consequences of their drinking than are their male peers.

Other sex differences in adolescent health problems relate to differences in sequelae. For example, sexually transmitted diseases have their highest incidence during adolescence, and female adolescents are at risk for the most severe of their complications—sterility. The risk of pregnancy as a result of adolescent experimentation with sexuality has already been discussed. Two preventable infectious diseases should also be considered. First, rubella now occurs in its highest incidence among adolescents, and immunosurveillance data suggest that about 5% of those who have been immunized in infancy no longer have protective titers.[19] As these youngsters approach their childbearing years, it is vitally important that their immunity be established by checking titers and by reimmunizing, if necessary. Second, the toxic shock syndrome, typically caused by the combination of a superabsorbant tampon and *Staphylococcus aureus,* occurs more frequently in adolescents than in adults.[20] Female adolescents should be informed about its prevention.

In summary, physicians who undertake the care of adolescent women will be successful to the extent that they allow adequate time for the patients to express their concerns, convey a message of respect for their privacy and emerging maturity, and are willing to maintain confidentiality. A knowledge of the biology of puberty and of psychosocial development will facilitate caring for adolescent women and improving their health status.

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Women and Medicine

Cesarean Section, 1988—To Have or Have Not!

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The rate of cesarean sections has risen from 3% to 5% in the 1950s to a projected 24% of all births in the United States in 1988.[1] While there have been notable increases in the rate of cesarean sections in other countries, the US rate far outstrips theirs. For example, Norway had a cesarean section rate of 2.2% in 1970; in 1983, the rate was 9.4%. This compares with a 20.3% rate in the US during the same year.[2] At least two of the reasons for the substantial increase in the number of deliveries by cesarean section are expectations and fear. Every patient—and, indeed, every physician—expects a perfect result from the pregnancy: neither the child nor the mother should suffer damage. This is a perfectly understandable expectation of a result that, in the main, occurs with more frequency today than 20 years ago because of the increasing use of antibiotics, blood transfusions, ultrasonography, and newborn intensive care. In a relatively small proportion of pregnancies, however, something may be imperfect either in the development of the child or in the maternal outcome. The expectation is that if the pregnancy is delivered by cesarean section, there is a higher probability that there will be no maternal or fetal damage. The fear is that if a patient has not been delivered by cesarean section and there is an imperfection, the physician will be blamed for not doing a cesarean section, with a high probability of subsequent litigation. Such litigation, even if unsuccessful, is emotionally taxing on those members of the health care team who are involved.

An Increased Use of Cesarean Section

Are the expectations warranted? The possible relationship between the increase in the rate of cesarean sections and the reported decrease in perinatal mortality has been examined in a number of ways. Williams and Chen found that in California 81% of the decline in the perinatal mortality rate was due to birth-weight-specific mortality.[3] The decrease in mortality rates was significantly faster for cesarean deliveries than for vaginal births. Thus, they concluded that while the major decrease in perinatal mortality was due to the introduction of neonatal intensive care, the increase in the cesarean section rate had some positive effect on the decline in perinatal mortality. Pearson, on the other hand, examined the cesarean section rate in a city and county hospital from July 1973 to June 1982.[4] During that period, it increased from a low of 5.8% to a high of 8.2% and the perinatal mortality rate dropped from 35 to 18 per 1,000 live births. The increase in the cesarean section rate for this hospital began about 1978, when the perinatal mortality rate had already fallen from 35 to 18 per 1,000 live births. Thus, Pearson argued that the increase in the cesarean section rate, which was small, was associated with a virtually level perinatal mortality and that the drop in perinatal mortality had occurred before the increased use of cesarean sections.

When considering the possible benefits of increasing a cesarean section rate, the consequences must also be considered. These fall into three distinct categories: detriment to the mother, detriment to the fetus, and the increased costs in health care. The maternal risks include increases in maternal mortality and morbidity. Maternal mortality in the United States has fallen to extremely low levels. In 1985 the adjusted maternal mortality rate was 7.9 per 100,000 live births,[5] but delivering a child by cesarean section seems to increase the mortality. Statistics from a study by the Commission on Professional Hospital Activities showed that the maternal mortality in 1978 was 9.8 per 100,000 vaginal deliveries, but it was 40.9 per 100,000 cesarean section deliveries.[6] Evrard and Gold showed similar data from Rhode Island.[7] Petitti and associates found a two to three times higher death rate from cesarean section than from vaginal births in California.[8] Their study has been criticized, however, because maternal deaths due to cesarean section may have been underreported. Even though the risks of cesarean-section-associated death for the mother are 2 to 20 times greater than those of vaginal deliveries, the frequency of the event is low. Thus, many mothers feel that cesarean section is just as safe as vaginal delivery.

The prevalence of the second complication to the mother, puerperal morbidity, clearly increases substantially following cesarean section. This increase is about five to ten times that for vaginal birth.[9,10] Puerperal morbidity is influenced by whether or not a patient has been in labor, the duration following rupture of the membranes, and the number of vaginal examinations. The causes of the morbidity include endometritis, perimetritis, urinary tract infection, and, rarely, pulmonary embolus and pulmonary infection.

The adverse effects of cesarean section to a fetus are relatively minimal. They include the possibility of fetal laceration and the development of the respiratory distress syndrome following an elective repeat cesarean section. The latter situation rarely occurs if the date of pregnancy has been

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properly ascertained and pulmonary maturity determined before doing the cesarean section.

In terms of cost to the health care system, Banta and Thacker estimated the net additional cost of doing a cesarean section in 1977 to be $2,300.[11] These figures are increased today because of the increased cost of medical care. In addition to the cost of hospital care, a physician's fee for doing a cesarean section is roughly a third higher than that for a vaginal delivery.

Some Indications for Cesarean Section

There are four categories of indications for cesarean sections that account for most of the increased rate. These include dystocia or failure to progress in labor, repeat cesarean section, breech presentation, and fetal distress.

Dystocia

Except for elective repeat cesarean sections, dystocia accounts for the largest increase in the cesarean section rate. In a study reported by 1,527 US and 171 Canadian hospitals involving 130,000 abdominal deliveries, 43% of the cesarean births were done for dystocia or failure to progress in labor.[12] Hibbard[13] and Mann and Gallant[14] have shown that about a third of the increase in the cesarean section rate is attributable to this diagnosis. Apparently obstetricians are reluctant to expose mothers or fetuses to prolonged labor because of the general feeling that it leads to complications for both. There is little, if any, evidence, however, to suggest that any increase in fetal damage occurs in labors lasting 24 hours or less. Unfortunately, many obstetricians feel that an eight-hour trial of labor is sufficient. An adequate trial of labor depends on a patient's degree of cervical effacement and dilation when the monitoring of labor begins—noting the frequency and intensity of uterine contractions, the stage of labor, the presence or absence of intact membranes, and the position of the child coming through the birth canal. A woman with an undilated, uneffaced cervix and intact membranes may need 24 hours or more of adequate uterine activity to take her through the latent phase of labor. On the other hand, a patient with ruptured membranes having good uterine contractions—that is, 50 mm or more of mercury in intensity with a frequency of three per ten minutes—at 7 cm of dilation may be considered an excellent candidate for cesarean section after two to three hours of labor that fails to progress. Many physicians feel that the second stage of labor (from complete cervical dilation to delivery) should last no longer than 30 to 60 minutes. Here again, the information on fetal damage in second-stage labors lasting longer than two hours is lacking. In a national collaborative study, no increase in neurologic damage occurred to those infants subjected to longer than two hours in the second stage of labor.[15] In a study by Cohen, there was no change in neonatal mortality or morbidity as measured by five-minute Apgar scores when infants were subjected to a second stage of labor of two to three hours.[16] Clearly, the definition of a normal and safe progression of labor needs to be elucidated and disseminated.

Some increase in the cesarean section rate can be attributed to physicians' reluctance to use forceps to deliver an infant. This reluctance seems to be unjustified. Recent studies show that there is no increase in fetal morbidity with the use of low forceps.[17,18] The American College of Obstetricians and Gynecologists recently issued an opinion—Opinion #59, February 1988—that redefines the application of forceps: An outlet forceps delivery is used when the scalp is visible at the introitus without separating the labia, the fetal skull has reached the pelvic floor, the sagittal suture is in the anterior-posterior diameter or in the right or left occipital anterior-posterior position, and the fetal head is at the perineum. According to this definition, rotation cannot exceed 45 degrees. A low forceps delivery is defined as applying forceps when the leading point of the skull is at station +2 or more. A mid-forceps delivery is used when the head is engaged but the leading point of the skull is above station +2. There is no difference in perinatal outcome when one compares deliveries in which low forceps or outlet forceps were used and spontaneous deliveries.[19]

Elective Repeat Cesarean Section

The largest number of cesarean sections done under a single category is that of repeat cesarean sections. In 1916 Craigin published a dictum that any woman who has had a cesarean section should have all her future children by cesarean section.[20] His purpose was to lower maternal mortality, and his reasoning was valid at that time because classic (corporeal) cesarean sections were being done and subsequent labor would result in rupture of the uterus with almost uniform fetal death and frequently maternal mortality. The situation in 1988 has changed in a number of respects. First, most cesarean sections are now lower segment cesarean sections, primarily transverse, but some vertical. The classic cesarean section is rarely done. We have blood transfusions, antibiotics, rapid cesarean section, and continuous monitoring of uterine activity and the fetus. All of these assure greater safety even if a lower segment cesarean section should rupture. In fact, no English-language literature in the past ten years reports maternal deaths attributable to a rupture of a lower segment cesarean section when the patient's labor was managed in hospital. This has led many to feel that a trial of labor is acceptable for a woman who has previously had a cesarean section, particularly if it was a low transverse one.

Lavin and colleagues reviewed 25 trials of labor after cesarean section from 1950 through 1980 and concluded that "vaginal delivery after cesarean section appears to be relatively safe."[21] These studies indicate that the frequency of a successful vaginal delivery after cesarean section, while depending somewhat on the indication for the cesarean section, will be between 70% and 80%. They also show that it is perfectly safe to use oxytocin stimulation with careful monitoring and that epidural or other conduction anesthesia can be used with safety. Despite the safety and success rate, vaginal delivery after cesarean section is seldom practiced in the United States.[22] Using national hospital discharge survey data, Placek and Taffel showed that, while the frequency of vaginal births after a cesarean section increased between 1980 and 1985, it went from only 3.4% to 6.6%.[22] The reasons for this slow acceptance in the United States of vaginal delivery after cesarean section, when the rate is 32% in Hungary and 43% in Norway,[22] are somewhat difficult to explain. Many obstetricians report that they discuss the possibility of a trial of labor with their patients who have had cesarean section but are met with a negative response. The patients say that they like the convenience of setting a time when their child will be born and the possibility, especially if the previous trial of labor was long and difficult, of having a painless delivery.

If we are ever going to increase the number of vaginal births after cesarean section, we must emphasize the negative aspects of cesarean section—that is, the increased maternal death rate and maternal morbidity—and the positive aspects of vaginal birth after cesarean section. There have been no deaths from rupture of the uterus reported in the American literature, and fetal safety can be assured with continuous monitoring of the heart rate. It is, of course, critical for a physician who is going to conduct the trial of labor to be fully cognizant of the signs of impending rupture, which include not only alterations in the fetal heart rate but any unexplained vaginal bleeding, any unexplained uterine pain or tenderness, and, finally, a lack of uterine activity.

Breech Presentation

Breech presentation occurs in about 3.5% of all pregnancies and, with the prevailing feeling that all infants presenting in breech should be delivered by cesarean section, accounts for an important increase in the cesarean section rate. The impression that infants presenting in breech who are delivered by cesarean section have a lower mortality and morbidity is based on retrospective studies.[23-25] More recently, randomized prospective studies have indicated that some infants presenting in breech can be delivered safely by the vaginal route. Collea and co-workers showed that a term infant in frank breech weighing between 2,500 and 3,800 grams can be safely delivered through a normal-sized maternal pelvis.[26] Gimovsky and associates had a similar finding in infants presenting in nonfrank breech.[27]

Another method of reducing the incidence of cesarean section for breech presentation is to reduce the frequency of breech presentations. This can be done by using external version. Wallace and associates have shown that about 70% to 80% of infants presenting in breech after 37 weeks of gestation can be safely and successfully turned to a vertex presentation and that greater than 95% will remain in a vertex when the mother enters labor.[28] External version can thus decrease the incidence of breech presentation at birth to 1% to 1.5%. It is important that the mother have a well-relaxed uterus and that the heart rate be monitored, both before and after the version, to assure that the infant has encountered no difficulty.

Fetal Distress

Fetal distress accounted for about 15% of the increase in the rate for cesarean deliveries from 1970 to 1978.[6] Zalar and Quilligan, reporting on the experience at Los Angeles County Hospital, found that in 1970, 1974, and 1976, about 12% of the primary cesarean sections were done for fetal distress.[29] Haverkamp and colleagues and Leveno and co-workers have shown a higher cesarean section rate for fetal distress when the use of continuous electronic fetal monitoring is compared with intermittent auscultation of the fetal heart rate.[30,31] Kelso and associates also showed an increase in the rate of cesarean sections associated with continuous fetal heart rate monitoring—not with true distress.[32] Thus, the mere practice of continuous fetal heart rate monitoring has been associated with an increase in the cesarean section rate, both for apparent fetal distress and for prolonged labor. This increased rate can be modified somewhat, as has been shown by Haverkamp and colleagues, by further evaluating the fetus.[33] These authors used fetal scalp sampling. Others have shown that fetal scalp stimulation or sound stimulation (or both) associated with acceleration of the fetal heart rate can be used to rule out fetal acidosis in the presence of a normal fetal heart rate pattern.[34,35] To reduce the incidence of cesarean section for "false" fetal distress, physicians must have a thorough understanding of fetal heart rate patterns and use advanced techniques such as scalp sampling or fetal stimulation to diagnose true fetal distress. Abnormal fetal heart patterns do not necessarily mean the fetus is distressed, or vice versa.

Summary and Conclusions

There has been at least a fivefold increase in the rate of cesarean sections during the past 20 years. A portion of this is justified and may be associated, to some degree, with the reduction in perinatal mortality. The soaring rates being reported, however, would appear to be unjustified. It is important that hospitals monitor their cesarean sections closely, examining them on a case-by-case basis to determine whether or not alternate methods of delivery would have accomplished the same goals of maternal and fetal safety and well-being. A number of safe and effective mechanisms can be used to cut down on the incidence of cesarean sections. These include a more careful diagnosis of dystocia, an increased number of vaginal births after cesarean section, selective vaginal delivery of infants presenting in breech, antepartum external cephalic version of the breech, and a careful and accurate diagnosis of fetal distress. All of these should be considered by thoughtful physicians giving obstetric care.

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Women and Medicine

Pregnancy Complications of Physicians

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Studies indicate an increased risk of adverse late pregnancy events, such as preterm labor and preterm delivery, for practicing physicians. These adverse pregnancy outcomes also occur among pregnant women who work long hours with high levels of psychological stress, a mechanism most likely related to catecholamine and posturally mediated alterations in uterine blood flow. Further evaluation and research into the epidemiology of physicians' pregnancies are needed because of the increasing number of women physicians in their childbearing years.

(Katz VL, Miller NH, Bowes WA Jr: Pregnancy complications of physicians, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:704-707)

Greganti and Fletcher, in an editorial on physician pregnancies, said, "We are concerned that the number of complicated pregnancies among women on our housestaff may have been more than expected."[1] This sentiment has been held by obstetricians throughout the medical community. As the number of women physicians has increased, the number of published reports verifying the accuracy of that concern has also increased.

Analyzing physician pregnancies is important for several reasons. First, the number of physician pregnancies in the United States alone makes for a numerically significant "high risk" group. Additionally, physician pregnancies are a model for understanding the effect a person's environment can have on health and disease. An understanding of the problems of physician pregnancies may elucidate important aspects of the pathophysiology that can be extrapolated to other pregnant women. Finally, confronting the fact that physicians may have more problems with pregnancy than most other women disturbs the facade of immunity to disease that pervades the medical profession. We review current information about physician pregnancies and make some suggestions about solving the problems these physicians may face.

The Number of Physician Pregnancies

A growing number of physicians are women. Half of the residents in training in Canada and Great Britain are women, as are nearly 40% of physicians in training in the United States.[2,3] Schwartz calculated that by 1991 there will be 80,000 physicians in their childbearing years.[4] Surveys project that as many as 90% of women physicians desire children, and two thirds of currently practicing physicians have children.[4-6] A recent study reported that the average married physician has between two and three children and that half of women physicians had a child during training.[7] We estimate that during a three-year residency, at any given time one of every six married women will be pregnant; between 10,000 and 15,000 physician pregnancies will occur in the United States per year by 1991. If the percentage of women in training in the US rises to 50% (as has been projected) the number of physician pregnancies will increase proportionally. Thus, physicians represent a substantial subgroup of the pregnant population.

Are Physicians at High Risk for Adverse Pregnancy Outcomes?

The question of whether physicians are at increased risk for adverse pregnancy outcomes has not been answered satisfactorily. A large prospective analysis of hundreds of physician pregnancies has not been done. Information concerning pregnancy outcomes of physicians is available only from retrospective studies, surveys, and questionnaires, with their inherent methodologic limitations. Almost all of these reports do, however, reflect an increased risk of complications for pregnant physicians.[4,8-11]

Schwartz retrospectively studied 72 pregnancies among 34 physicians and medical students during a four-year period and found a rate of abruptio placentae ten times greater than expected and a 12% incidence of preterm labor.[4] Through a questionnaire, Grunebaum and co-workers studied 454 pregnancies among obstetricians.[8] When the pregnancies were separated into categories of resident and nonresident, these investigators found an 11.6% rate of low birth weight and an 8% incidence of intrauterine growth retardation among residents. These rates are much higher than would be expected in a population matched for age and socioeconomic status. These rates also compared with a 2.6% incidence of low birth weight and 1% incidence of intrauterine growth retardation for babies born to women physicians after residency. Birth weights were significantly lower for those babies born during a woman physician's residency than either before or

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after training. As a result, these infants would be more susceptible to neonatal illness.

In a prospective analysis of the relationship between occupation and pregnancy outcome, McDonald and associates surveyed 56,000 pregnancies.[10] There was a decreased risk of miscarriage and stillbirth among 295 physicians and dentists compared with the overall population.

Miller and colleagues did a historical cohort study of a ten-year period at a university hospital obstetric practice to determine if physician pregnancies were associated with more adverse pregnancy events than pregnancies of women of similar socioeconomic status.[11] A total of 67 pregnancies of practicing physicians were matched one to three with 201 nonphysicians' pregnancies for age, race, educational level, parity, and date of delivery. Alcohol and tobacco use and adequacy of prenatal care were controlled for in statistical analysis. Adverse events were defined as preterm labor, preterm delivery, low birth weight, abruptio placentae, toxemia, and perinatal mortality.

Overall, physicians were at a 1.8 times increased risk for at least one adverse outcome in pregnancy. These included, for physicians, a 4.0 times increased risk of preterm labor, defined as contractions and documented cervical change, and a 2.3 times greater likelihood of preterm delivery. The cesarean delivery rate, incidence of fetal distress in labor, mean birth weight of term infants, and Apgar scores of less than 7 at five minutes were found to be similar between the physician and nonphysician groups, however. Physician pregnancies showed a trend ($P < .1$, $P > .05$) towards more meconium-stained fluid. There was no difference between the two groups in the use of obstetric technologies, with the exception of the number of ultrasound examinations.[11]

Thus, the available literature regarding physicians' pregnancies seems to show an increase in the late pregnancy complications of preterm labor, preterm delivery, low birth weight, and abruptio placentae. Of special interest is the outcome of preterm labor because this can lead to preterm delivery with its attendant neonatal morbidity and mortality. Although eight physicians and six nonphysicians in the Miller study had preterm labor, only three physicians delivered preterm infants. All other infants were delivered at term after successful treatment of the preterm labor.[11] This underscores the importance of close obstetric monitoring and treatment.

Early pregnancy complications such as miscarriage or congenital anomalies are even less well studied than late ones. Studies of pregnant women's exposure to anesthetic gases, toxic chemicals, radiation, and a variety of infectious diseases suggest all cause an increased risk of adverse pregnancy events.[12-17] Many of these studies are methodologically flawed, but most pregnant physicians are aware of the proposed associations and are likely to take precautions in these areas. Obstetric histories in patients studied by Miller, Schwartz, and McDonald and co-workers did not indicate increased miscarriage or stillbirth rates.[4,10,11]

Why Physicians Might Be at Risk for Adverse Late Pregnancy Events

Several aspects of a physician's job might put her at risk for an adverse pregnancy outcome. Authors who have noted the increased incidence of adverse outcomes in late pregnancy have suggested that these may be caused in part by the amount of work that physicians do.[4,8,11] While physicians are likely to take precautions to avoid exposure to gases, chemicals, and infections, limiting exposure to strenuous work may be more difficult. Most pregnant physicians work long hours.[4,6,8,11] One study indicated that women residents worked an average of 95 hours per week.[6] After residency training, long hours and long shifts are still the norm rather than the exception.[4,18] The relationship between maternal work and pregnancy outcome has been studied extensively. While no association has been found between employment that is not strenuous and adverse pregnancy events, pregnant women with strenuous jobs—excessive work hours, lifting, and being upright for long periods—have been found to be at increased risk for preterm labor, preterm birth, low birth weight, abruptio placentae, toxemia, intrauterine growth retardation, and perinatal mortality.[19-26] This is the constellation of adverse pregnancy outcomes particular to physicians. The severity and frequency of adverse outcomes increase as the number of hours and physical stress increase.[8,10,20,21,24]

The emotional and physiologic stresses of medicine are incomparable to other occupations and add particular hazards to physician pregnancies. Not only is the job of being a physician stressful, but when a physician becomes pregnant, extra stresses are added.[1,3,6,27,28] In a study by Sayres and associates, 67% of residents reported that their pregnancies had created resentment among their peers and 57% of physicians said that their pregnancies caused administrative difficulties as well.[6] Psychological stress has been documented to be a risk factor for preterm labor and preterm delivery.[29-32] Thus, physicians' work can be considered both strenuous and stressful, two factors that are associated with prematurity, low birth weight, and placental abruption.

Pathophysiologic Mechanisms of Stress on Adverse Outcomes

The constellation of adverse pregnancy outcomes to which physicians seem susceptible is most likely caused by a decrease in uterine blood flow, mediated by catecholamines and postural effects. An upright posture leads to a decrease in cardiac output, with altered uterine blood flow. Blood is shunted to the extremities, and fluid tends to pool in the lower extremities during long periods of standing.[33-35] Changes in the fetal heart rate pattern, an increased maternal heart rate, and decreased maternal blood pressure and venous return have been documented,[33,34] as well as decreased uterine blood flow. The result is a decreased availability of nutritional substrates, leading to lower birth weights.

The magnitude of the changes in uterine blood flow is proportional to gestational age and is greatest at term. The theory that altered uterine blood flow is related to low birth weight is corroborated by studies that have shown that women who stopped working in the last weeks of pregnancy or who stopped exercising in the third trimester have had infants of greater birth weight compared with controls.[36,37] Thus, decreases in uterine blood flow may be a significant factor contributing to low birth weight in many physician pregnancies.

When psychological stress is added to the long hours a physician works, a further decrease in uterine perfusion may occur. Occupational stress leads to a greater production of catecholamines. Timio and colleagues measured urinary excretion of adrenaline (epinephrine) and noradrenaline (norepinephrine) and observed an increase proportional to the

degree of psychological stress in the workplace.[38] Catecholamines cause vasoconstriction in the uterus by adrenergic receptors in uterine vessels.[39,40] Excessive vasoconstriction is associated with abruption and placental infarction. Chronic vasoconstriction may lead to intrauterine growth retardation.[41]

The relationship between excessive work and premature labor may involve changes in the levels of progesterone.[32] Progesterone is the primary hormone responsible for uterine relaxation. We also speculate that long periods of standing could lead to greater pressure on the uterine contents by the cervix, thus leading to increased uterine contractility and premature labor. The decreased plasma volume associated with being upright could stimulate increased production of oxytocin with decreased intravascular volume.[35] Thus, several factors of a physician's job have a negative impact on the uteroplacental unit.

Areas for Future Research

Several areas of research are needed to confirm the hypothesis that the increased incidence of late adverse pregnancy outcomes among physicians is related to strenuous work and increased stress.

- An evaluation is needed of physicians' pregnancy outcomes that quantifies work hours, call schedules, and subspecialties in an effort to determine actual work intensity. Such a study must be appropriately matched with a control group for factors known to affect pregnancy outcomes.
- A similar evaluation concentrating on physicians' pregnancies during residency training is also necessary.
- A comparative evaluation of biochemical markers of stress—urinary catecholamines, for example—may help substantiate the role of stress in pregnancy outcomes. Similarly, evaluating the placentas of pregnant physicians, looking for histologic changes due to chronic hypoxia and chronic vasoconstriction, would add to our understanding.

Recommendations

Several recommendations have been made to help decrease the risks for adverse pregnancy outcomes in physicians.[4,8,11] These call for decreased work hours, changes in night call schedules, and lengthened maternity leave, all justified and appropriate recommendations. As stated previously, the greatest factor leading to poor pregnancy outcomes among physicians seems to be time spent working, particularly during late pregnancy. Unfortunately, changes in schedules are often difficult to enact in the milieu of a training program or with a physician just starting practice.

There are several simple suggestions that we give to pregnant physicians in our practice. At the University of North Carolina at Chapel Hill, we consider pregnant physicians at high risk for adverse outcomes and follow them more closely than low-risk pregnant patients. At the initial prenatal visit, we discuss what is known about physicians' pregnancy outcomes. We explain the increased risk of prematurity and preterm labor and emphasize the relationship of prematurity to long working hours and increased stress. We make a point of documenting gestational age as early as possible by both ultrasound study and cervical examination. Physicians receive a cervical examination at 24 to 26 weeks' gestation to detect silent dilatation. The cervix is inspected at that time, and the vaginal flora is evaluated. If abnormal vaginal flora or discharge is found, it is treated.

Physicians are counseled again at the end of the second trimester regarding signs of premature labor. Early premature labor—contractions before cervical change—is usually treatable, whereas premature labor once cervical dilatation has occurred is a much more difficult process to interrupt. We attempt, therefore, to sensitize pregnant physicians to uterine contractility. If there seems to be an increase in contractions, we ask them to notify us. We ask residents to try to schedule their least stressful rotations during a pregnancy's "window of vulnerability"—26 to 34 weeks. We recommend elevating the legs whenever possible during the day and tell pregnant physicians to take a lunch break with their feet up. If contractions occur at a rate of greater than four per hour during the late second or early third trimester, we ask these women to take a few days of bed rest and stop night call. After uterine irritability stops, they may resume an 8 AM to 5 PM schedule with careful observation.

Another problem for physicians is decreased oral intake during the working day. Because relative dehydration can cause an increase in uterine contractility, we ask our patients to drink 6 to 8 ounces of liquid, not coffee, per hour. We ask physicians to drink from a water fountain every time they pass one. If bleeding or decreased growth occurs at any time, bed rest is recommended.

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Cinderella

Medium: Bronze

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Women and Medicine

Women Without Health Insurance

Links Between Access, Poverty, Ethnicity, and Health

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In the United States, inadequate health insurance is a problem for men and women; for the young, the not-so-young, and the elderly; the poor and nonpoor; and for persons of all ethnic groups. It is especially problematic for particular groups, and certain gaps appear to be widening. In this article we focus on the problem of lack of health insurance for women. The problem is particularly severe for women of ethnic minorities, who are overrepresented among poor women. We describe the characteristics of the inadequately insured population and discuss the links for women between poverty, insufficient insurance coverage, inadequate health care, and poor health status.

Women are more likely than men to be poor and to live longer. These demographic and economic factors account for additional health care needs for women beyond special needs related to reproduction. A lack of adequate coverage for women and the economic problems that accompany insufficient access to care and aggravate its deleterious effects on health need to be addressed by public policy.

Characteristics of the Uninsured

From 9% to 18% of the entire population has insufficient health insurance.[1-3] The figure of about 37 million persons, or 15% of the population, is widely accepted as a current estimate of those who are uninsured for all or part of a given year.[4,5]

A greater proportion of the nonelderly population is uninsured because almost all US elderly are covered by Medicare. A recent study of census data has shown that 22% of Californians younger than 65 years are uninsured.[3] Other Western states with similar demographic and economic trends as those found in California may also exceed the national average for uninsured persons.

Considering all age groups together, the female population is slightly less likely than the male population to be completely uninsured (14.5% versus 14.8%, respectively).[5] This is probably explained by the higher proportion of women living below the poverty line as heads of household and therefore qualifying for Medicaid. Working women, however, are more likely than working men to be in low-paying positions (M. Tolchin, "Minority Poverty on the Rise Even as White Poor Decrease in the US," *New York Times,* September 1, 1988) or to be employed in the service sector, or both; such positions tend to have limited health insurance and other benefits.[6] Overall, the uninsured are primarily low-income working persons and their dependents.[3,7]

Young adults and children have the highest rates of uninsured status for both sexes.[2,3] For women, therefore, the problem of lack of health insurance is most severe in childhood and during the reproductive years. Of women aged 15 to 44 years, 17% are estimated to have no private or public health insurance.[8] During that age interval, women's need for health services is substantially higher than men's because of reproductive health needs, including perinatal care and contraception. Furthermore, the reproductive years are the time period when women's health most affects society as a whole, by determining the health of the next generation.

Severe tightening of restrictions for Medicaid qualification has resulted in a loss of coverage for many poor women and their children. Medicaid at one time provided coverage for 65% of the poor in the United States, but recent figures estimate that only 38% of the poor are covered by Medicaid nationally and in some states less than 25% of the poor are covered.[7] By 1982 California and many other states had discontinued Medicaid coverage for "medically indigent adults"—that is, those whose financial resources were judged insufficient to cover medical costs but who do not qualify for a categoric welfare program such as programs for the blind, disabled, or families with children. Federal regulations in 1984, 1986, and 1987 have tended to reverse some of the tightened eligibility criteria for pregnant women and young children.[9,10] A recent report by the congressional Office of Technology Assessment called attention to the problem of obstacles in the Medicaid application process

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itself that may provide disincentives to technically eligible women to enroll, which thus results in more women being uninsured.[9]

The problem of inadequate health insurance is most severe for minority women. For both sexes, non-Latino whites are far more likely than minorities to have private health insurance. In the US in 1982, 21.2% of nonelderly blacks had no private or Medicaid coverage compared with 13.5% of nonelderly whites.[5] In California, blacks, Latinos, and Asian adults are all more likely to be uninsured than are non-Latino whites.[3]

Incomplete insurance coverage for minority women is of particular concern because ethnic minorities, especially black women, endure a disproportionate burden of illness and thus have greater needs for health care. Blacks in the United States have twice the rate of infant mortality compared with whites.[11] Overall, age-adjusted mortality rates are higher for minority women than for their white counterparts.[12] While the incidence of breast cancer appears to be higher among white women, breast cancer survival rates are higher for white than for black women, who tend to be diagnosed at more advanced stages of disease.[13] Death rates from heart disease are twice as high for black as for white women. The black:white ratio for stroke mortality in women is 2.5:1.[13] When compared with white women, black women also have higher mortality rates from cirrhosis and diabetes mellitus and are at higher risk for tuberculosis, hypertension, and anemia. Mexican-born US women have a 38% excess death rate from diabetes compared with non-Latino white women.[14]

Insured Women May Have Incomplete Coverage

The problem is not only a lack of health insurance for women but insufficient coverage for women who do have insurance, whether Medicaid, Medicare, or private insurance. Although most Medicaid enrollees are children and young women, a relatively small proportion of Medicaid funds is spent on them. Nearly 67% of Medicaid expenditures go to cover costs for the elderly—primarily long-term care not covered by Medicare—or costs for care of the blind, mentally retarded, or physically disabled.[15]

Women who are theoretically covered for specific benefits under programs such as Medicaid may have difficulty obtaining care. For example, Medicaid reimbursement rates for delivery may be a third to half the rates of reimbursement by private insurance.[16] Because of Medicaid's inadequate, slow, and procedurally burdensome reimbursing of providers, it has become increasingly difficult for women on Medicaid to find private physicians who will provide their obstetric care. Nationally, 44% of physicians providing obstetric services will not accept Medicaid.[8] The West tends to have a lower proportion of obstetricians accepting Medicaid than do the Northern and North Central states, but it has a higher proportion than the South.[16]

While Medicare covers almost all elderly persons of both sexes, it provides little coverage for ambulatory or preventive services. Medicare provides almost no coverage for long-term care, which accounts for a significant portion of the health care needs of the elderly. Many elderly persons become impoverished as a result of nursing home expenses, ultimately becoming dependent on Medicaid.[15] The impoverishing effect of Medicare's lack of coverage of nursing home care affects women more than men because of their greater longevity. Elderly women are more likely than men to lack private health insurance to supplement Medicare because these benefits are often lost after divorce or the death of a spouse.

Private insurance often provides incomplete coverage. For both sexes, private health insurance increasingly comes with rising premiums, deductibles, copayments, and exclusions. Most indemnity plans favor acute curative or hospital care over ambulatory and preventive care, although most women, particularly young women, have a greater need for the latter. Many women with insurance have inadequate coverage for maternity care: 9% of women who have private insurance have policies that exclude coverage for maternity care.[8] Most (58%) health insurance plans for full-time employees impose waiting periods on women before they qualify for maternity care. More than half of those have waiting periods of three or more months.[8]

Inadequate Insurance Coverage Is Associated With Inadequate Health Care

A lack of sufficient insurance coverage affects women's use of health care. In general, uninsured persons use ambulatory medical care less than their insured counterparts.[1] Data from a large national survey show that the use of preventive services by older women is especially diminished: While the percentage of women having a Pap smear and the percentage of women having a breast examination by a physician during the previous year increased for women with insurance between 1976 and 1982, they declined for uninsured women.[17] Lack of insurance, most prevalent among socioeconomically disadvantaged women, was found to be the strongest predictor that women between 45 and 64 years of age would fail to receive appropriate screening tests.[17] Uninsured women, compared with insured women, have a relative risk for inadequate screening of 1.60 for blood pressure checkups, 1.55 for cervical smears, 1.52 for glaucoma testing, and 1.42 for clinical breast examinations.[18]

Uninsured women and women on Medicaid are less likely than insured women to obtain timely prenatal care.[2,16] A recent study by the US General Accounting Office (GAO) found that 63% of uninsured or Medicaid-covered women received incomplete prenatal care as defined by the Institute of Medicine's criteria.[16] The GAO study sample included women from diverse communities in the West and in the Midwestern and Eastern states. Pregnant women on Medicaid initiate prenatal care later than privately insured women and have an average of 8.7 prenatal visits compared with the average of 10.5 visits for all pregnant women.[8]

For pregnant women without sufficient private health insurance, many factors tend to delay a timely initiation of care. Even for the women who can meet eligibility criteria, the process of applying for Medicaid is lengthy, and it can be difficult to find a provider who will accept Medicaid. With limited options for care from private providers, and the closure or reduction of services of many community clinics in the past ten years,[4] the remaining publicly funded programs are increasingly operating beyond capacity.

For uninsured women and those on Medicaid, the strains on existing public programs mean not only longer waiting times to secure an appointment but on-site congestion with increased waiting-room delays, harried providers with insufficient time for each patient, and little opportunity to provide personalized care. All factors combine to create additional

disincentives to seeking care and obstacles to high-quality care (Table 1).

Inadequate Health Care Is Linked With Poor Health Status

Inadequate health care, especially for children and for pregnant women, is documented to result in poorer health status. A particularly clear example is the association between prenatal care, low birth weight, and infant health status. Initiating prenatal care after the first trimester is associated with adverse pregnancy outcomes and especially low birth weight, which in turn is associated with serious short- and long-term morbidity and mortality.[19] Appropriate prenatal care is associated with improved birth weight distribution for all ethnic groups. The US infant mortality rate is among the highest of the industrialized countries, including many countries with far lower per capita incomes. A total of 17 states in the United States, including Alaska, Arizona, California, Idaho, Montana, New Mexico, Utah, Washington, and Wyoming, experienced increases in infant mortality in 1985.[20] Between 1984 and 1985, neonatal mortality rose in Arizona, California, and Colorado and black neonatal mortality rose nationally.[20]

Failures in primary prevention, for both sexes, are thought to account for 15.1% of premature deaths in the United States.[21] It is estimated that a 30% decrease in the mortality from female breast cancer is obtainable with breast self-examination, physician examination, and mammography.[21] Cervical screening every three years can lead to a 70% to 95% reduction in cervical cancer mortality.[21]

Demographic and Economic Factors Increase Women's Health Care Needs

Data on health care use show that, in general, women use more health care services than do men. Women have higher rates of illness, have more days of disability, and use more health services than men, even when pregnancy-related services are controlled for.[11] These differences have been ascribed to "women's diseases" (breast cancer, menstrual irregularities, and other gynecologic conditions), to the effect of women's illness behavior (more willingness to admit symptoms or to visit a physician), or to sex-specific differences in access to care or response of the health care provider.[11] We think that important demographic and economic differences between women and men provide additional explanations for women's greater use of health services and greater reported disease incidence.

Most important, poverty is associated with a poorer health status for both sexes,[20,22-24] and more women than men are poor. Almost 78% of the poor in the United States are women and children, and three quarters of the elderly poor are women.[11] Almost a fifth of women aged 65 or older live below the poverty level ("The New Poorest," *The Economist,* September 13, 1986, p 24).

Minority women are far more likely to be poor than their non-Latino white counterparts. A third of blacks and more than a quarter of Latinos live in poverty. The US Census Bureau recently reported increases in the percentages of blacks and Latinos living below the official poverty level, while white poverty declined slightly (M. Tolchin, "Minority Poverty on the Rise Even as White Poor Decrease in the US," *New York Times,* September 1, 1988).

Another trend aggravating the economic differential is the increasing number of households now headed by women. Between 1960 and 1982, the number of families headed by women more than doubled, and these families were 4.5 times more likely to be poor than a male-headed family or that of a married couple.[6] More than half of families headed by Latino or black women live in poverty in the United States. Women are heads of household for 23% and 41% of Latino and black families, respectively ("The New Poorest," *The Economist,* September 13, 1986, p 24).

Elderly persons of both sexes have more disability and use more health services than the nonelderly. Women live on average eight years longer than men.[11] The continuing increase in the longevity of women has its own economic consequences and contributes heavily to women's burden of medical disability. At the close of the 20th century in the US, it is estimated that 35 million persons will be aged 65 or older and, of these, 20 million will be women.[11]

TABLE 1.—*Insurance Problems of Women*

14.5% completely uninsured
Greater poverty and longevity of women create additional health care needs
Minority women have less insurance and more illness
Lack of coverage for ambulatory preventive care, including unmet needs during reproductive years
Bureaucratic barriers to receiving Medicaid
Many ob/gyns will not care for pregnant Medicaid patients
Long waiting periods before insured women are eligible for pregnancy benefits
Some insurance plans (9%) exclude pregnancy care

TABLE 2.—*Health Problems of Women Due to Inadequate Insurance Coverage*

Less screening for breast cancer, high blood pressure, cervical cancer, and glaucoma
Delayed prenatal care with associated adverse perinatal outcomes
Higher rate of impoverishment due to inadequate Medicare coverage for nursing home care

Conclusions

A lack of sufficient health insurance coverage is a serious problem for women, especially for poor and low-income working women, minority women, and women of reproductive age (Table 2). Many insured women, including pregnant women with private or public coverage and elderly women, are underinsured. Inadequate health insurance is associated with inadequate health care, which is in turn associated with worsened health status.

Women have special needs for health care, associated with reproductive health. The greater poverty and the greater longevity of women are also factors that determine additional health needs for women, independent of obstetric and gynecologic issues. The relationships between women's poverty, health insurance coverage, and health status imply that those with the greatest health care needs are least likely to have financial access to care.

The inadequacy of coverage for perinatal care has been particularly well documented. Because perinatal services tend to be relatively inexpensive and politically popular, insufficient perinatal services for large numbers of women in this country suggest a far more extensive problem of inadequate care for women and for the entire population.

Differences between whites and minorities in health in-

surance coverage and in socioeconomic status are widening. Ethnic gaps are also widening for key health status indicators such as maternal mortality, low birth weight, and neonatal mortality.

As long as there are women or men who are underinsured or completely uninsured, it will be important to study and to document differences in health care use and in health status measures related to health insurance coverage. Currently, routine reporting of most health data does not include markers of access to care such as health insurance coverage or socioeconomic status. This lack of data makes it difficult to determine the relative contributions of poverty, a lack of access to care, and of other factors to the striking ethnic differentials in health status for women. The absence of relevant information then serves to hide the issues that require decisive action at the policy and program levels.

A rational response to the unmet health needs of inadequately insured women will require not only scientific data but political will. It will require addressing not only lack of access to medical care but the broader social inequities that are barriers to health for women, minorities, and all poor persons.

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In Balance

Medium: Mahogany

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Women and Medicine

A Forecast of Women's Health and Longevity
Implications for an Aging America

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Our society has witnessed an unprecedented and unanticipated increase in life expectancy in the 20th century. Over the past 15 years, mortality rates have declined at a rapid rate among those older than 65 years. The drop in mortality from 1965 onward followed two decades of virtually stationary death rates for men and slowly declining ones for women, a drop that caused worrisome inaccuracies in social programs that rely on projections, such as Social Security. Because of this dramatic change—"a demographic transition"—new and more accurate data on longevity and health are becoming available.[1] Analysts are trying to develop models to better forecast the population patterns of the next 30 to 50 years. These forecasts will have major implications for planning health care services, health care financing policies, and priorities for research.

In this article, we will review the current data on longevity of women. We will describe the status of health in old age by examining national data on morbidity and, equally important, on disability. We will look at changes in women's roles that are related to health status and, finally, review some special issues for disease prevention that are relevant to women.

Life Expectancy and Mortality

Since population records have been kept, a century or more, the life expectancy of women has always exceeded that of men. Even though some recent statistics indicate that the longevity gap is narrowing somewhat,[2] there is no reason to think it will close altogether. In 1900, a man who reached the age of 65 could expect to live 11 more years, and a woman aged 65 could expect to live 12 more years. By 1985, men turning 65 could expect to live 14.5 more years and women turning 65 could expect to live 18.7 more years. The biologic or environmental reasons for this differential life expectancy have yet to be elucidated by scientists, even though this subject has created a great deal of scientific interest, particularly among those concerned with understanding the basic mechanisms of aging and its regulation.

At birth, every cohort has a small excess of male children, but because of a higher death rate for males all across the life span, women far outnumber men in the older age groups. In 1986, for all those 65 and older as a group, the ratio was 68 men to 100 women.[3] The sex ratio declines rapidly with increasing age, as shown in Figure 1.

The group older than 85 years, called the "oldest old," is probably the most important for health care planners and other social policymakers because of steep increases in the prevalence of chronic illness, disability, and dependency in this group. This is not a small group, currently numbering 2 million and growing at a faster rate than any other segment of the population. By the year 2020, there may be as many as 5 million persons older than 85 years. The US Census Bureau's recent publication, *The Centenarians,*[4] points out that the number of persons older than 100 years in the United States increased in just five years from 15,000 in the year 1980 to 25,000 in 1985. The forecast is that this number will increase to 110,000 by the year 2000 and perhaps 300,000 to 500,000 by the year 2050. If these predictions are correct, and if patterns from the past continue, as many as 80% of these centenarians will be women.

Our aging society is not only growing older but becoming increasingly heterogeneous. In successive subgroups older than 65, the general pattern of social characteristics is similar, but the pattern becomes more pronounced. The oldest persons are socially and economically diverse; yet, as a group they have a disproportionately high number of low-income persons, especially women, many of whom are living with someone other than a spouse or by themselves, with a large proportion living in institutional settings.

The longevity differential results in an increasing risk of widowhood among elderly women, leaving them with meager financial resources. The current cohort of women older than 65 receives very little in Social Security or pension benefits because few of them worked outside the home. The result is that while the incomes of both oldest men and oldest women subgroups are lowest, women are more likely to be below the poverty level, especially among minorities.

Not only are most women widowed by the time they reach 65, but by the time they reach 75, more than half live alone. The differences between men and women are dramatic with regard to living arrangements. In 1980, 74% of older men but only 36% of older women had a spouse in the household. At age 75 and older, it was 65% of men but only 19% of women.

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Poor women of advanced old age who live alone are at the greatest risk of being confined to an institution. This is reflected in the fact that of the 1.5 million residents of nursing homes, the average age is older than 80 years and more than two thirds are women.

Active Life Expectancy

Even though elderly women as a group are at great risk of economic and social disadvantage, most of them (and most men) are enjoying good health and good levels of functioning further into old age than was true of persons in earlier decades. Most people today look forward to an active and vital old age; it is disability and dependency they dread and that pose the most pressing demands for medical and long-term care.

The big question facing demographers and epidemiologists is whether the gains in healthy life expectancy are greater than the gains in overall life expectancy. That is, how much of our added years of life can we expect to be relatively healthy and independent? One important study done in Massachusetts[5] found that with increasing age, there was a smaller percentage of "active life expectancy" and a greater percentage of time spent in a state of chronic illness, disability, and dependency (Figure 2).[6] In this study, women had the longer life expectancy in each age group but they had only a modest advantage over men in "active" life expectancy in the 65- to 69-years age group and no advantage in the older age groups. According to the data, while women live longer, the age that disability begins is the same as for men and thus the period of predeath morbidity is increased for women.

Other analysts predict a "compression of morbidity," where life expectancy will reach a maximum around age 85 or 90, with disabling chronic illness prevented or delayed, thus shortening the period of time spent in dependency.[7] This latter model is highly speculative and does not explain observed sex differences.

To evaluate these two contradictory models and to understand their implications for women's health require a look at the specific causes of death and of disability in women.

Causes of Mortality

The three leading causes of death—heart disease, cancer, and stroke—account for about 75% of all deaths in people older than 65 years and are about the same for men and women. For all three causes of death, progress in prevention, as well as in diagnosis and treatment, has delayed both the onset of the disease and death from the disease. Deaths from cardiac disease, cancer, or stroke have not been entirely prevented, but they happen much later in life than they did 20 or even 10 years ago. In the oldest, the over-85 group, both men and women die more frequently of stroke than of malignant disorders, while cardiovascular disease remains the number one cause of death. Progress in risk factor modification and in the treatment of these diseases will continue to increase life expectancy, but it is not likely that the major causes of death will change much in the next 20 years.

Morbidity and Mortality

Figure 3 contains survival curves representing mortality, disability, and morbidity. The outermost curve (mortality) shows the progressive number of persons dying as a cohort ages. The lowest curve (morbidity) represents the probability of surviving to a given age free of chronic disease. The area labeled A under this curve represents the number of years that a person in this cohort could expect to survive free of disease. Morbidity refers to the presence of disease but does not imply anything about the impact of disease on a person's functional level or quality of life.

Morbidity statistics have been taken from national surveys and other sources in which disease categories, either self-reported by patients and their families or taken from medical records, indicate the prevalence of certain kinds of diseases.

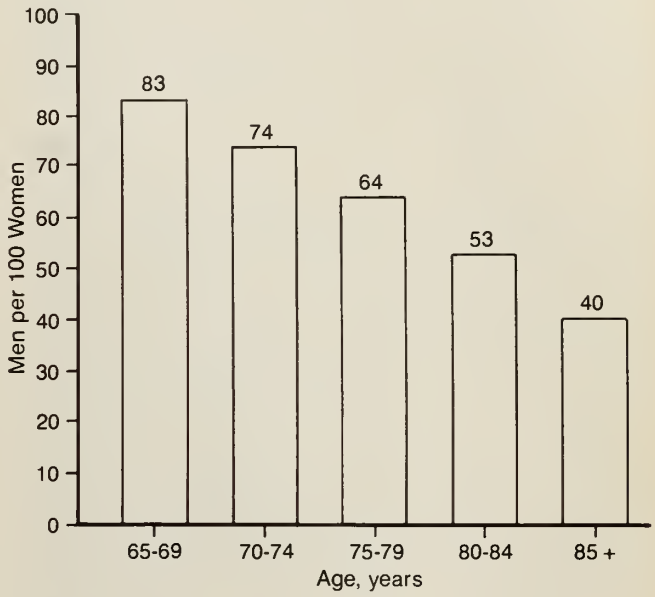

Figure 1.—The graph shows the number of men per 100 women by elderly age group in 1986 (from US Bureau of the Census[3]).

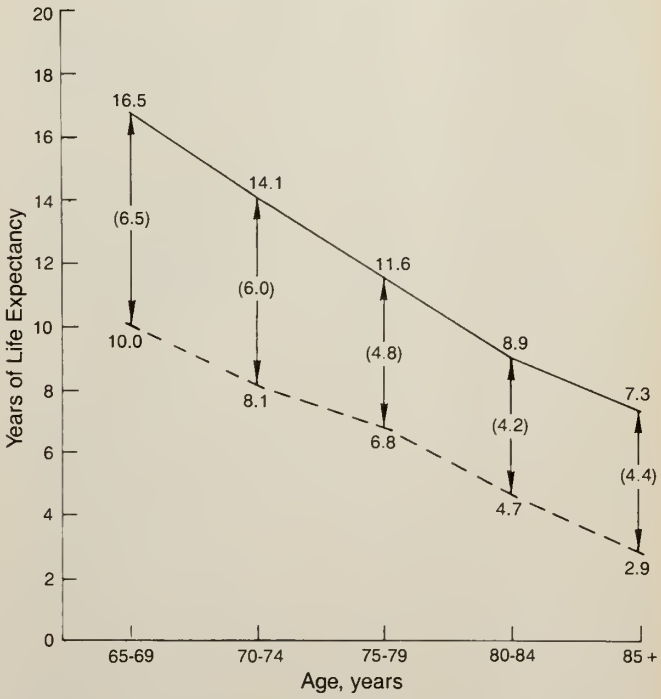

Figure 2.—The graph shows the average years of active life expectancy between 1974 and 1976 **(dashed line)** in relation to life expectancy in 1974 **(solid line)**. The numbers in parentheses indicate the average number of years for each group spent in a state of chronic illness, disability, and dependency (from Statistics for Health Policy[6]).

The most commonly reported illnesses among women, as well as among men, are chronic, predominantly nonfatal diseases. In national surveys of the population older than 65 in an institution, arthritis is the most frequently reported chronic condition (50%), with hypertension (40%), hearing impairment (30%), and visual impairment (10%) also listed as significant contributors to morbidity.[8]

Disability

Returning to Figure 3, the middle curve labeled disability shows the probability of surviving to a given age free of serious chronic disability. The implication is that morbidity—that is, the presence of disease—can exist without significantly impairing a person's functional level. At some point a person's activities are limited to such a degree that that person thinks of herself or himself as disabled. It is assumed that disability emerges as the result or the progression of some underlying disease processes, but social, economic, and psychological factors inevitably influence the degree to which a person is disabled by disease, and it is therefore important to keep such factors in mind.

There are two additional areas in Figure 3. The first, the area between the morbidity and disability survival curves labeled B, defines the number of years that a person can expect to live with the presence of disease but free from disability. The second area defined by the disability curve, labeled C and lying between the disability curve and the mortality curve, represents the number of years that a person can expect to live in a chronically disabled state. Thus, the total area under the disability curve (areas A and B) represents the period of "active life expectancy." The period represented between curves B and C is that of disabled or dependent life expectancy. Certain disease processes that do not cause death but do cause functional impairment will be most significant during this period, such as Alzheimer's disease, Parkinson's disease, arthritis, visual or hearing impairments, and fractures due to osteoporosis, especially of the hip and vertebrae. Obviously, the existence and duration of these kinds of disabilities will have an important impact on the need for long-term care services.

Disability is usually measured by the number of days disabled, degree of activity limitation due to chronic conditions, or self-rated health status. In some studies of the elderly, measures of functional state such as the ability to perform activities of daily living—those related to basic hygiene, feeding, and mobility—are used. A somewhat different but related measure is of "instrumental" activities of daily living in which higher levels of function, including such things as shopping, cleaning, and managing finances, are tallied.

Some of these instrumental activities traditionally have been carried out by women and, thus, when a man becomes disabled, he can go on living "independently" if his wife does the shopping and cleaning and cooking.[9] For a woman, particularly a woman living alone, a stroke that impairs her ability to shop or clean can make an enormous difference in her ability to go on living independently. Thus, there is role bias in a number of studies of disability. Because the measures used in such studies were not differentiated for men and women, disability rates for men may be understated.

Using disability measures, can we detect a trend in the health of older American women in the past few decades? Studies of trends for both American men and women[10] have found that health profiles have worsened at all ages, especially in the group older than 65. Policy analysts attribute this phenomenon to a combination of better treatment of acute illness that allows more people to survive with disability and the fact that more recent studies have provided more extensive data. For the United States population at large, national surveys show increased short-term disability rates for both acute and chronic conditions, longer restrictions per acute condition, rising percentages of persons with chronic activity limitation, higher prevalence rates for chronic diseases that are the leading causes of death, and higher prevalence rates for common nonfatal chronic diseases.

The fact that health profiles have worsened has an especially great impact in the elderly population, where lower mortality rates since the 1960s have been documented and where, as a result, there is a longer period of survival during which time people are at risk for a number of the chronic disabling disorders of old age. In addition, an earlier diagnosis of chronic disease and a greater willingness to acknowledge disability may contribute to the reports of an increased prevalence of short- and long-term disability. All of these factors together can be responsible for the increasing morbidity rates.

Women's Roles and Health Status

Tomorrow's elderly will include many of today's working women. In a recent study of the relationships between women's social roles and health status for the period from the mid-1960s to the late 1970s, three major social roles were examined: employment, marriage, and parenthood.[11]

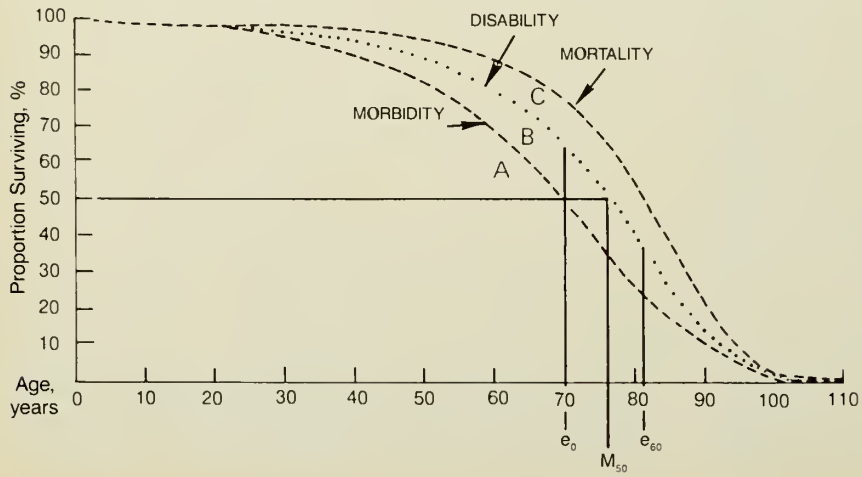

Figure 3.—The graph shows the percentage of persons surviving in relation to morbidity, disability, and mortality (from Statistics for Health Policy[6]). A full discussion of the meaning of the curves and the areas below the curves (labeled A, B, and C) is given in the text. e_0 and e_{60} are the number of years of autonomous life expected at birth and at age 60, respectively. M_{50} is the age to which 50% of women could expect to survive without loss of autonomy.

Among both white and black women younger than 65 years, bad health is concentrated among the nonemployed, nonmarried. Contrary to popular belief, women with the triple roles of worker, spouse, and mother were the most healthy in both races. At the other extreme, those women who have neither children, job, nor spouse have the worst health status. These patterns do not distinguish cause and effect; that is, healthier women might be those who are more able successfully to marry, bear children, and work outside the home; it is also possible that the lack of a job and spouse may be stressful factors that might lead to deleterious health consequences.

Population health trends reflect a complex interplay between medical and psychosocial realities. Dramatic role changes have occurred for women in the past few decades, but those role changes have not yet affected the elderly age group. Some parts of the demographic revolution are yet to come, where a dramatically increasing number of women will survive into old age with relatively good health and vigor, bringing with them the knowledge and skills of occupations and professions. In future decades, we may see equally as dramatic social role changes among elderly women as we presently see among younger women.

Much research has shown that satisfaction with one's main work role, either job or housework, is a strong predictor of good health and that overall life satisfaction is linked to a longer life.[12] That autonomy and choice of life-style are related to health in old age has long been thought and is shown in various studies of adaptation to retirement. It may be that flexible and innovative approaches to work, such as recognition by the Social Security system or other pension plans that homemaking is work, could add to the options for healthy elderly women and thus contribute to their well-being.

The Frail Elderly

While increasing life expectancy is accompanied by continued health for most people, the percentage of persons who require major medical care, nursing care, or assistance in activities of daily living increases dramatically after about age 75. In nursing homes about 75% are elderly and 60% to 70% are women. As mentioned earlier, the group at highest risk of being confined to an institution are very old women, widowed, poor, and living alone. The determinants of the need for institutional care are not simply levels of disability but also the availability of informal support systems that might allow a person to be cared for in the home.

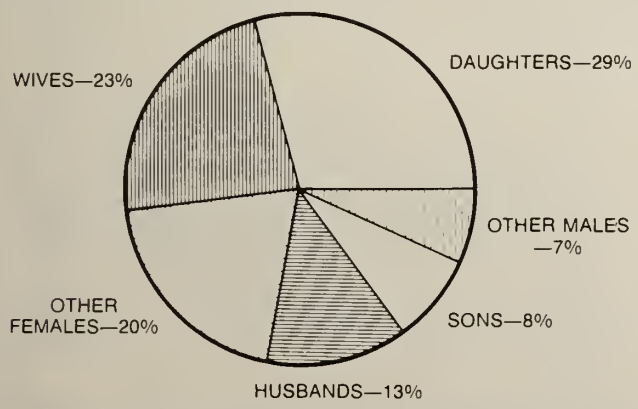

Figure 4.—The diagram shows the distribution in 1982 of informal care givers by their relationship to the elderly care recipient. The care-giving population includes primary and secondary care givers (from House Select Committee on Aging[14]).

For every elderly person in a nursing home in the US, there are about two to three times as many of exactly the same functional state who are being cared for by informal care networks, usually composed of family members.[13] It is also the case that women, primarily daughters and daughters-in-law, are the persons who provide this care, regardless of the sex or even the direct blood relation with the elderly person in need (Figure 4).[14] With increasing longevity, this fact carries with it some serious problems. It is no longer uncommon for a 90-year-old woman to be cared for by her 70-year-old daughter or daughter-in-law. There are also many instances of women in their 90s caring for a 70-year-old daughter who may be immobilized by stroke or hip fracture. Elderly people living alone are at greater risk of going into an institution than similarly disabled people of the same age who are living with one or more other persons.[15]

The Future

Demographic trends will influence the availability of informal sources of care for elderly women. Future cohorts of older people in this country will be larger than the present cohort, and thus the "burden" of caring for frail old people will increase. As the population ages, potential informal care givers, such as spouses or adult children, will be older themselves and will possibly be less able to care for elderly relatives.

In addition, families are having fewer children and middle-aged women are more often working. This will leave fewer women at home to provide care. It already accounts in part for the rapid increase in the number of elderly women living alone and the increased need for institutional long-term care.

Prevention

If the chronic disabling conditions of old age could be prevented or delayed and if the human life span is fixed at approximately 85 to 100 years, we could look forward to the phenomenon of the compression of morbidity. In that theoretic context, it is predicted that improvements in life-style will both delay the onset of disability and reduce the prevalence of morbidity from chronic disease—thus, a compression of morbidity at older ages. People would then die at the end of a natural life span without first experiencing a long period of decline.[16]

Existing data suggest that two of these premises are incorrect. Clearly the major causes of disability and morbidity in very old age are chronic degenerative neurologic diseases, such as Alzheimer's and Parkinson's diseases, and chronic musculoskeletal illnesses such as osteoarthritis and osteoporosis with fractures. Currently, little is known about either the etiology or methods of preventing any of these diseases. Therefore, the hope that life-style changes would influence these diseases is not based on sound data.

In addition, it is possible that life span itself may be increasing, in addition to life expectancy.[17] Life span is defined as the biologic natural limit to human life, while life expectancy is the average number of years lived by a cohort. If life span itself is increasing, albeit at a slower pace than life expectancy, then longer periods of disability would be predicted as people live longer.

Thus, increasing life expectancy will probably lead to a virtual "pandemic" of chronic diseases and states of dependency.[18] The increases in the prevalence of chronic condi-

tions due to advances in medical technology have been the failures of success. The number of very old people is increasing rapidly, and the average period of diminished vigor will probably also increase. Chronic disease will probably occupy a larger proportion of the life span, and the needs for medical care in later life are likely to increase substantially.

Prevention—A Model

One of these chronic disabling diseases, osteoporosis, is beginning to be clarified by research that focuses on preventing its most disabling and life-threatening consequences, namely bone fracture and particularly hip fracture. In 1980, about 200,000 people, whose median age was 79, suffered hip fractures, and increased incidence is correlated directly with increased longevity. Recent studies on osteoporosis show that moderate exercise can delay age-related bone loss, even in older women, especially when combined with estrogen replacement treatment. Brody has shown that if hip fracture itself could be delayed only five years overall, the incidence of hip fracture would decrease by 50%.[19]

This is an important observation for two reasons. First, it reflects the fact that elderly people have many chronic illnesses, and by "preventing" or "delaying" death from one cause, a person is exposed to the risk of death from another cause, such as heart disease or cancer. Second, it suggests that one need not entirely prevent the underlying disorder from occurring, but, rather, through training and environmental manipulation, as well as meticulous medical care and the avoidance of unnecessary medications, it is possible to prevent the fall that often results in hip fracture—the fall that results in entry into an institution and being unable ever to walk again. Thus, to delay the onset of the first hip fracture by five years would effectively prevent fractures, for it would allow many people to die of other causes without succumbing first to the long-term disability of hip fracture. This same principle might apply to other disabling diseases, such as Alzheimer's disease or osteoarthritis, if we knew how to delay their onset.

Conclusion

What can we anticipate in the future? Barring unforeseen disasters such as environmental catastrophes or major wars, we can expect a continuation of the increase in life expectancy in this country. While we do not understand everything about its cause, we have no reason to believe that the greater longevity of women will change. If current trends in cardiovascular mortality continue, it is possible that men will live longer and catch up somewhat to women. Morbidity will be delayed, but probably not significantly "compressed."

Extending life expectancy will probably result in ever larger numbers of both economically and physically able very old people and chronically ill, dependent persons. Two major fears about such long lives relate to the health and economic status of old people. There are considerable differences among persons in lifetime economic and work experiences, level of educational attainment, living arrangements, health practices, and health care, all of which have implications for the well-being of persons when they reach old age and for the cost to society. Catastrophic illnesses and illnesses of long duration are a significant economic threat, even to the aged persons who have good economic resources, because old persons have little opportunity to replace their assets once they are spent.

Given our current medical knowledge, we can expect to see an increasing number and proportion of older women suffering from the chronic, nonlethal, disabling diseases of old age, primarily degenerative neurologic and musculoskeletal disorders. This will lead to the need for a tripling of our long-term care capability, including institutional care and community-based resources for home care.[20] A critically important need is a shift in medical training to a greater emphasis on long-term care.

There are many important areas of uncertainty in these forecasts. We hope to see major advances in understanding the etiology of diseases such as Alzheimer's disease and osteoarthritis. It is entirely possible that new knowledge could lead to effective preventive or ameliorating treatments. Further advances in molecular biology may lead to more specific and effective treatments for cancer, thus diminishing or even eliminating the disability and mortality caused by breast cancer, lung cancer, leukemia, colorectal cancer, and the other major malignant disorders of old age.

In this social context, we can hope that society will find a way to maintain a relatively affluent economy and to offer equal access and equal payment to women and men of all ages, based on their qualifications and capabilities rather than on their age or sex. If these kinds of advances were to occur, we might see a very different society in the year 2020 or 2030. There might be more older people, particularly women, in major positions of political and business leadership. There might be a greater social commitment to both long-term care insurance and regulations that protect families from exhausting their personal and financial resources in caring for their frail older members. Women could then help support their children's college educations, be productive in the economy, and still be assured that their frail elderly relatives are receiving good care.

There is no doubt that there are many problems and challenges that lie ahead. There is also no doubt that the aging of our society is the result of the success of our civilization. An increasing number of older people should be seen not only as a burden but as a challenge for a humane, affluent, and successful society. It will take foresight, courage, and vision, however, to turn this challenge into positive realities and, for example, to avoid discriminatory policies in which people are denied health care simply because of their advanced age.[21]

Whatever social, political, and biomedical realities accompany the next demographic transition, one thing is clear: the problems of the aging society will rest increasingly on women. The solutions, too, may depend on the experience and expertise of its women.

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⁜ ⁜ ⁜

Intensive Care

Dorothy smells sweet in her dying.
Her infection, pseudomonas, consumes her
like a crumbling stick of honey incense.

Sparked from rough coals of cancer dug
from her belly, the smouldering spreads,
burns in sheltered corners in her lungs.

We force air into Dorothy through a hole
in her neck—another surgery, another
wound that will not heal.

We forget a simple rule:
don't chase cancer
with a knife.

⁜

Dorothy, I never knew you whole.
Comatose from the first day, you have lain
these weeks with eyes turned in on

who can tell? Pain,
or memory, or the bright
glow of your dying?

Maybe the sweet combustion
of bacterial growth is a scent
that centers you in that old, deep brain.

If I knuckled your chest where the bones
show thin, you would only flex
your wrists in a limp salute,

or your jaw would quiver open-close-
open-close, the way wild animals grimace
for the taste of prey.

⁜

Your men are gone.
Father, husband, sons who waltzed with you
have faded into the wallpaper roses.

There is no one to lead you in this last
number. We are two girls in white left
to learn the final steps together.

It has always come down to this:

women teaching women how to live.
Dorothy, my grandmother, my child,
I feel too young for this mothering.

Gloves off, I take your hands
burning with infectious fire
that beats in your blood,

hot sparks pumped round and
round by the tired iamb
of your heart.

⁜

It is late afternoon—time enough for tea,
and little biscuits, and crumbs that fall
to the pink napkin in your lap.

Flowers bloom in corners sheltered
from the swish of passing dancers.
Musicians blow notes under the swaying palms.

Feel the beat, Dorothy, one-two-
one-two, like wild animals
pacing in a cage.

A sweetheart waits in the knife-edge
shadows of the potted palms,
and when the music stops—

when *the music stops, Dorothy—*
he will ask you
for the next dance.

⁜

The air folds into you
like layers of perfumed
tissue paper.

Here is a red rose
to burn in the ash
of your hair.

I tell you, Dorothy,
it is time
the music stopped.

Valerie Berry, MD
Palo Alto, California

Women and Medicine

Screening for Cancer

ANTHONY B. MILLER, MB, FRCP(C), *Toronto*

Screening has proved effective for only two cancer sites, the breast and the cervix uteri. Only for these, therefore, should screening be a part of routine clinical practice. The degree to which screening is effective depends on whether appropriate groups are screened. For cancer of the breast, current evidence justifies mammographic screening every two years only from the age of 50, continuing at least to the age of 70. The place of breast self-examination and physical examination of the breasts is under investigation, but these procedures should probably be used in all women after the age of 40. For cancer of the cervix, nearly maximal efficacy is obtained by screening sexually active women every three years from the age of 25 to 60. Older women who have not been screened regularly should be screened. Other screening techniques to detect cancers, such as the rectal examination, sigmoidoscopy, and fecal occult blood tests for colorectal cancer, are still experimental. Organizational and other difficulties will prevent screening programs from making a major contribution to reducing overall cancer mortality by the year 2000. If organizational problems can be overcome, however, screening may control invasive cancer of the cervix and make a major contribution in reducing breast cancer mortality in the future.

(Miller AB: Screening for cancer, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:718-722)

There are many issues relating to screening for cancer at a number of sites. I will discuss these issues and summarize the present knowledge about screening for cancer in women. In doing so I shall draw on the conclusions of the International Union Against Cancer (Union Internationale Contre le Cancer; UICC) project on screening for cancer.[1-4] I shall then consider the prospects for an important contribution of screening to control cancer in women from now to the year 2000 and beyond.

What Is Screening?

Screening is the process by which we administer tests designed to detect disease at an earlier stage in its natural history than we would find in the course of normal clinical practice. Some make a distinction between case finding, which is testing for disease in a physician's office during a visit initiated for another purpose, and mass screening—administering tests to the whole population or to a substantial proportion of the whole. This distinction has become blurred because many tests, such as the cervical smear, are usually administered in a physician's office. Yet, the same criteria for their application should be applied as for tests administered at special centers. The same ethical principles should apply in both circumstances, namely, the test must be both effective and as free from hazard as possible because those eligible for screening will usually be healthy and asymptomatic and hazards could affect large numbers, whereas benefits usually will accrue only to a few.

How Do We Decide Whether or Not Screening Is Effective?

It is useful to evaluate screening in terms of the test and the screening programs in which the test is given. A screening test should be of adequate sensitivity and specificity, as established in screening circumstances. Sensitivity is the ability of a test to detect disease, expressed as the proportion of those who have detectable disease who test positive. Specificity is the ability of the test to exclude disease, expressed as the proportion of those free of the disease who test negative. Case detection alone is not sufficient to justify introducing screening into private practice. That requires confirmation that, as a result of applying the test, the incidence or the mortality from the disease, or both, is reduced, and this, in turn, requires that we evaluate the effectiveness of screening programs.

The UICC project concluded that randomized controlled trials could evaluate the effectiveness of screening programs.[1] In practice, this means that any screening test shown to be valid should be incorporated in a screening program and the program evaluated by means of a controlled trial. Trials of screening require a major investment in resources, and not all aspects of screening can be evaluated in this way. Indeed, there has never been a controlled trial of screening for cancer of the cervix, even though it is thought that screening for that condition is effective. The investment required to apply screening in the general population, even if restricted to certain age groups, is so large, however, that it

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ABBREVIATIONS USED IN TEXT

BCDDP = Breast Cancer Detection Demonstration Project [United States]
BSE = breast self-examination
FOB = fecal occult blood
HIP = Health Insurance Plan
NBSS = National Breast Screening Study [Canadian]
UICC = Union Internationale Contre le Cancer (International Union Against Cancer)

now seems unwise to permit any compromise of this principle.

Physicians usually assess the outcome of cancer treatment by comparing survival rates. The potential effects of screening biases are so considerable, however, that physicians cannot assume effectiveness based on improved case survival. These biases are lead time, length bias, selection bias, and overdiagnosis bias. Lead time is the extent to which diagnosis is advanced by the screening test. Length bias is the tendency for intermittent screening to detect the slow-growing cancers and to allow the rapidly progressing cancers to slip through the screening net. Selection bias refers to the fact that health-conscious women tend to participate in screening programs. This can be a major problem, for example, in screening for cancer of the cervix because high-risk women tend not to be screened. Overdiagnosis bias refers to the fact that some screening tests pick up lesions that might never have presented if the women had not been screened. There are some indications that this could be a problem in mammography screening. Thus, screening is effective if it reduces mortality (deaths applied to the whole population rather than the cases) or it detects a precursor of the disease, as for cancer of the cervix, by reducing the incidence of clinically invasive cancer.

Even when a program has been extended to the general population, we are not exonerated from the obligation of monitoring it to assess its continuing effectiveness. In the future, primary prevention could make screening less cost-effective and improvements in therapy for clinically detected disease might make screening unnecessary.

Screening for Breast Cancer

There is good evidence that screening for breast cancer can reduce mortality from the disease.[4] The data that confirm this statement have come from two completed randomized trials[5,6] and three case-control studies.[7-9] Of these, only one, the Health Insurance Plan (HIP) trial, has shown any evidence of effectiveness in women aged 40 to 49 and only for those women with long-term follow-up.[5] All studies, however, showed that screening is effective for women aged 50 or older.

The HIP trial and the Utrecht study combined mammography and physical examination.[5,7] The other studies were based on mammography alone, though in the Swedish trial the screening process incorporated a visual examination of the breasts, and the women received a pamphlet that advised them to practice breast self-examination (BSE) and explained the technique.[6] A single-view mammogram was used in the Swedish trial (mediolateral oblique) and in Nijmegen (lateral) and a double-view mammogram in the other studies.[6,8] Xerography was initially used in Utrecht, but clinicians changed to film screen in 1980.[7] All other studies used film (HIP) or film screen. Screening was done annually only in the HIP study. In Utrecht the intervals were 18 months, 2 years, and 4 years; in Nijmegen screening was biennial, in Florence[9] every 2½ years, and in Sweden every 21 months in women aged 40 to 49 and every 33 months in older women. An indirect estimate of the optimal interval between screening is possible by determining the proportion of the expected incidence of breast cancer (measured in the control group or from other data) to actual cases in studies with a long interval between screens. Data from both the Swedish[10] and Nijmegen[11] studies indicate that screening every two years is satisfactory in women older than 50 years and annual screening would be better for younger women.

All the studies had a similar order of effectiveness: breast cancer mortality decreased approximately 40% in women aged 50 or older at five (HIP) to seven (Sweden) years after initial screening. This order of effectiveness can be achieved by mammography alone. Whether physical examination (and BSE) provides greater benefit in combination with mammography or whether they can substitute for mammography is being investigated in the Canadian National Breast Screening Study (NBSS).[12]

Although final results from the NBSS cannot be expected for some years, data on the detection of breast cancer and early mortality from breast cancer are available. The breast cancer mortality experience is complete for subjects who have participated in the first three years of the study, and life tables can be used to extend the curves to five years. Comparing the first three years of experience with the HIP study suggests a similar relationship of deaths to diagnosed cases in the women aged 50 to 59 but a much improved survival in women aged 40 to 49. This is similar to rates reported for the United States Breast Cancer Detection Demonstration Project (BCDDP), which have been claimed as evidence that modern screening is effective in women aged 40 to 49.[13] Yet, the NBSS control-group survival in this age group is at least as good. Rather than indicating a benefit from screening, such survival data indicate the effect of self-selection for screening, the effect of improvement in (short-term) survival from the use of adjuvant chemotherapy, or both.

In summary, both single-view mammography alone and double-view mammography combined with physical examination have proved effective. Current findings are insufficient to determine whether adding physical examination to mammography reduces mortality, or whether double-view as distinct from single-view mammography gives better results. Further, it is not clear whether mammography adds an appreciable extra benefit to screening by physical examination, a question under investigation in the Canadian study (NBSS) in women aged 50 to 59 on entry to the study.[12]

Only results of the HIP study so far have indicated that screening is effective in women aged 40 to 49. Further, even if benefit is assumed, calculations suggest that screening women in this age group is unlikely to be cost-effective.[14] Although none of the shorter term projects using more modern mammographic techniques have extended follow-up to the point at which, in the HIP study, apparent benefit in younger women began to be seen, they have lasted long enough to confirm that any benefit to younger women will be delayed compared with that in women older than 50. Why such a difference in mortality over time exists is still unclear. One possible reason could be the relatively poorer sensitivity of the screen. All three projects that have so far failed to show benefit in younger women (other than the HIP study) used

mammography alone. Time will tell whether the combination of physical examination and mammography in the NBSS will benefit women in the study aged 40 to 49 years.

The other screening test for which we currently have no evidence of effectiveness is breast self-examination. Several studies now in progress will eventually provide the evidence needed.[4] Clearly only BSE has the potential to improve the outlook for interval cancers, while its teaching has probably gone some way to diminish the false reassurance in the NBSS. The World Health Organization has concluded that only BSE can effectively provide an early diagnosis of breast cancer in many parts of the world.[15] We may, however, have to wait ten years or more before we find out whether this potential is real or illusory.

The UICC project, as had others,[16,17] emphasized the importance of high-quality mammography and the need for health care workers skilled in localizing and diagnosing the impalpable lesions found by mammography. In the NBSS, we found that to ensure high-quality images with adequate contrast and definition, we had to constantly attend to the details of positioning and compression, film type and screen, darkrooms, developing of film, and to kilovoltage, phototiming, and dosage. These aspects were supervised by a reference physicist. A reference radiologist also assessed the performance of the radiologists reading the films.

Given the currently available scientific evidence, what should a woman do about breast cancer screening and how should her physician advise her? The following points are certain:

- The only risks are those of unnecessary biopsy and false reassurance. In North America, only about one in five of the biopsies done as a result of screening reveals cancer. Improvements in our diagnostic abilities will eventually reduce this to the one in two claimed in the best Swedish centers, but our medicolegal system will probably keep the ratio higher. That is, it is usually felt to be safer to do a biopsy when in doubt rather than wait. False reassurance will be minimized if women and their physicians realize that interval cancers—those diagnosed between screenings after a test with normal results—occur at the rate of about 1 per 1,000. Finding these cancers early by breast self-examination is one of its main justifications. Modern mammography is safe. The risk of radiation-induced breast cancer is negligible in the age group for whom screening is normally considered (40 years or older).
- All women aged 50 or older should be screened regularly. Although the standard recommendation is for annual mammography and physical examination, the evidence from the European studies supports screening with mammography every two years.
- The mammography should be high quality and done by a group experienced in screening. High quality is not equated with high cost. An experienced group with the necessary volume of work to ensure quality control will not need to charge $100 or more to make a reasonable profit. Any facility charging more than $100 probably has such a low volume service that there are good grounds to doubt its efficiency and experience.

The following areas are considered controversial:

- In my opinion, evidence is insufficient at present to recommend screening for women aged 40 to 49, and no evidence points to a benefit from screening younger women, even those judged to be at high risk. It is possible that women younger than 50 will eventually be shown to benefit. Breast cancer is a disease with a long natural history. Many women in whom breast cancer develops in their 40s die of it in their 50s. The evidence available is that screening will not prevent the deaths from breast cancer that occur in women in their 40s after the disease is diagnosed in their 40s. It may, however, help the group with a longer history of disease. Individual physicians must judge whether to incur the costs now in the hope of a benefit later, or, as the probability of benefit is low, to delay the initiation of screening until a woman's 50th birthday.
- What about the use of physical examination and BSE in combination? There is no clear evidence in favor of either, though in the NBSS, the use of both contributed to the early detection of breast cancer. The costs in our hands were low—on the order of $12 for a physical examination by a specially trained nurse, who also taught BSE. The examiner must be sensitive to the signs of early breast cancer, which are far different from those of advanced disease with which most physicians are more familiar.[18] A possible compromise would be that women aged 40 to 49 would have an annual physical examination and practice BSE, providing the examiner has the necessary skills.
- Whether women perceived to be at high risk should receive special consideration depends on the degree of risk and a woman's anxiety about it. Only a person younger than 50 years with a family history of premenopausal breast cancer in a first-degree relative (mother or sister) can be regarded as at high risk. Such a person might wish to add an annual mammogram to physical examination and BSE.
- The question as to when to stop screening in older women is difficult to answer. In North America, the risk of breast cancer developing increases throughout life; therefore, it seems scarcely logical to stop screening at age 65 or even 69 years. The upper age limit in the screening studies ranged from 64 to 74 on entry. In the HIP and the Nijmegen studies, screening was less effective in women aged 60 or older than in women aged 50 to 59.[5,8] In the Utrecht study the reverse situation applied.[7] In the Swedish trial screening was equally effective in women aged 60 to 69 as in women aged 50 to 59, but less effective in women aged 70 to 74.[6] Although older women were included, the compliance with invitations to attend for screening was poor and the results were not analyzed. Perhaps this is a clue. If women are prepared to be screened in their 70s, they should be encouraged to do so. If, however, they have other pressing health problems, regular physical examinations of the breasts and the practice of BSE might be sufficient.

Screening for Cancer of the Cervix

The UICC project concluded that screening for cancer of the cervix was effective in reducing the incidence and mortality from the disease, but well-organized programs were both most effective and used fewer resources. In an organized program,

- The target population has been identified;
- Individual women are identifiable;
- Attention to communication, such as a personal letter of invitation, guarantees high coverage and attendance;
- Field facilities for taking smears and laboratory facilities to examine them are adequate;

• Quality control programs monitor how health workers take smears and interpret them;

• Facilities exist for diagnosing and for appropriately treating confirmed neoplastic lesions;

• A carefully designed referral system is in place to advise patients whose smears indicate abnormalities and to provide information to subjects about normal screening tests; and

• Criteria exist to evaluate and monitor the entire program.[2]

Except for health maintenance organizations, North American medical care completely lacks the first three organizational features. In contrast, the Scandinavian studies for screening for cancer of the cervix[2] have shown the importance of good organization. It is a paradox that we accept without question a routine in which our dentist can recall us for a yearly examination, but we do not expect this of our family physician or gynecologist.

The optimal frequency of rescreening and the appropriate ages to initiate and stop screening are controversial elements of cervical cancer screening programs. The UICC project benefitted from the results of a study of the International Agency for Research on Cancer based on the records of a number of screening programs in Europe and Canada.[19] Patients for whom one or, preferably, two smears have been negative are at low risk for at least five years. Screening from age 25 to age 64 at three-year intervals gives 90% of the maximal protection and requires only 13 tests during a lifetime. Annual screening starting at age 20 gives just over 90% protection, yet requires a woman to have 35 tests in her lifetime. Thus, the yield from an annual screening compared with screening every three years is minimal. Eddy reached the same conclusion using his model[20] that underlay the American Cancer Society's recommendation for triennial screening.[21] The present recommendation, however, is for an annual smear, apparently to placate gynecologists rather than to ensure the maximal efficiency of a screening program.[22] Annual tests waste resources and lower the efficiency of laboratories, while doing nothing for indigent persons, who are those most at risk. To flood laboratories with a large volume of smears mostly testing negative will reduce the index of suspicion of laboratory workers and increase the likelihood that the rare positive test will be overlooked. Annual screening on the low-risk women who largely attend for annual tests does little to reduce mortality from the disease in the population. Those at risk for the disease are women who have been sexually active. Those at high risk are women who have had multiple sexual partners or whose sexual partner has had multiple partners. Many of these women have low incomes and no regular medical care. The concern for high-risk women is not whether or not they should be screened annually—in fact, there is no evidence that they should—but whether or not they are screened at all. An elderly indigent woman who has never been screened or who was screened many years before is at particularly high risk. A woman who has been screened regularly with no abnormality detected can be dropped from a screening program for cancer of the cervix once she has reached the age of 60.[23] But a woman in her 50s, 60s, or 70s who has not had this care is at high risk and should be screened. A recent study has shown that screening low-income elderly women is cost-effective.[24]

One of the arguments used to justify annual smears is that because it is desirable for women to have annual pelvic examinations, clinicians may as well do a smear at the same time. This argument is fallacious. There is absolutely no evidence that pelvic examinations will result in the earlier detection of other gynecologic cancers, nor can they be used as an argument for doing other screening tests, such as for colorectal cancer. Good screening tests are still being sought for detecting endometrial and ovarian cancer. The pelvic examination is not a good screening test.

Screening for Large Bowel Cancer

A number of controlled trials of colorectal cancer screening have been conducted or are in progress.[3] The earliest trials evaluated the use of rigid sigmoidoscopy as part of a multiphasic health screen. Although mortality from colorectal cancer was reduced in the study group, this was probably due to chance and not to the effect of sigmoidoscopy.[25] All the other trials are evaluating the effect of the fecal occult blood (FOB) test. Of these, two, both in the United States, have been running long enough for results on mortality to be expected, but to date they have not appeared. One of these, the New York study, has added the FOB test to routine sigmoidoscopic screening. The study was not randomized, however, and the results are likely to be difficult to interpret. The other study, in Minnesota, used the FOB test alone, annually in one group, biennially in another. Investigators have decided to resume screening in that trial (stopped by design a few years ago), so mortality results cannot be expected for some years. In the meantime it is clear, especially from the Minnesota trial, that a major difficulty with screening using the FOB test is that it lacks specificity, especially if the test specimen is rehydrated. Further, the procedure seems to lack sensitivity for adenomas. The evidence for this is somewhat indirect but relates to the postulated adenoma-cancer sequence. If an appreciable proportion of cancers arises from adenomas, and if the FOB test is capable of detecting adenomas, a reduction in the incidence of colorectal cancer should occur following FOB screening. This has not been the case so far in these trials.[3]

Health care workers tend to recommend screening for colorectal cancer largely on the basis of the results from mathematic models.[21] The UICC project workers reviewed the mathematic models in some detail and carefully considered the assumptions that underlie them.[3] We concluded that mathematic models should not be used as a basis for policy decisions unless and until their assumptions about benefit are based on hard data from controlled trials.

For these reasons, at present, screening for colorectal cancer or its precursors cannot be recommended as a public health policy.[3] The same conclusion was reached by the National Cancer Institute's year 2000 screening committee.[26] The current trials should provide some answers, but results cannot be expected for four to five years. In the meantime, dietary modification could have a favorable effect on the incidence of colorectal cancer,[27] and this could be a more cost-effective way of achieving control of the disease than screening.

Screening for Other Cancers

Of the ten principal causes of cancer death in women expected in the US in 1988, lung cancer is now first, breast cancer second, colon and rectal cancer third, pancreatic cancer fourth, ovarian cancer fifth, the leukemias sixth, the lymphomas seventh, cervical cancer eighth, stomach cancer

ninth, and liver and bile duct cancers tenth.[28] Screening tests are available for lung cancer and for stomach cancer. Screening for lung cancer using chest roentgenograms and cytologic analysis of sputum has been shown to be ineffective in randomized controlled trials.[1] Japanese physicians screen for stomach cancer using a specially developed air-contrast barium meal technique, but this technique is not recommended in North America.[3] Screening tests for cancers of the pancreas and ovary would be helpful, but none are yet available for routine use.

Prospects for the Future

Several aspects of current cancer screening programs lessen their effectiveness.[29] These include the unfavorable natural history of many cancers, poor organization of screening programs, and poor compliance with recommendations by those at risk. In addition, economic barriers to offering screening on a large scale, for example, mammography for breast cancer, or the absence of a valid and effective screening test pose problems. One class of screening test that is foreseen but not yet available could be based on monoclonal antibodies; such tests could be developed for ovarian cancer, for example.[2] There would have to be available sensitive diagnostic tests to localize the very small cancers that might be detected, unless the screening test could serve both functions, perhaps by being linked for diagnosis to a radiolabeled antibody.

Based on three more years of study results,[30] I have revised my previous projection[29] of the efficacy of screening programs. The percentage reduction for breast cancer mortality has been revised down from 25% to 20% because even if screening women aged 40 to 49 is eventually effective, it will have a delayed impact. Some may even regard a 40% reduction rate for mortality in older women optimistic, given the difficulties in persuading women to go for screening. If we can organize screening for the women at high risk for cancer of the cervix, mortality might be reduced by 60%, but time is running out to put the organization in place. For the other cancer sites, it now seems unlikely that any major impact will be achieved before the year 2000.

Screening reduces cancer mortality in women but not dramatically. Primary prevention is the optimal approach to the control of cancer. Yet, because primary prevention may take decades to achieve, screening offers a fairly rapid return for an appropriate investment and should remain part of our approach to cancer control.

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Breast Cancer—A Woman's Perspective

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This paper is bound to arouse controversy. It already has. No article in this special issue has been more thoroughly reviewed or had more widely divergent opinions. Some reviewers thought it expressed unrelieved anger; others felt it described the experience, perceptions, and feelings of many women with breast cancer. The paper seemed important to publish, however, because breast cancer is the second most common tumor occurring in American women.

It is important to note that the author is a successful teacher and health professional who has a full and active family and social life. She describes encounters with breast cancer in an uncommonly fervent and articulate way. These encounters have clearly left deep scars.

The essay is not scientific and not balanced in this issue by a paper by a woman who had a wonderful experience with breast cancer. Such a paper may never be written. Read on!

LINDA HAWES CLEVER, MD
Special Editor

Breast cancer is a "triple whammy." Any woman who has been treated for breast cancer knows that she is up against more than a medical problem. Not only does she have to absorb the enormous shock of acknowledging her own mortality, she also has to cope with compelling psychological concerns involving her appearance and sexuality. The medical and surgical treatment adds yet another facet to the unpleasant reality of a potentially life-threatening disease.

When I was diagnosed with breast cancer four years ago, I found myself plunged into a frightening world that was utterly unknown and totally out of control. Although I had good medical care, the experience of being a breast cancer patient was devastating. I had the advantages of being white, upper middle class, articulate, happily married, and well connected to the medical community with physicians who were willing to go to bat for me. If I had difficulty managing my illness, imagine the ordeal for women who are poor, passive, without family support systems, and sick, to boot.

All women with breast cancer face painful hurdles along the road back to health and normalcy. For me, there were several specific areas of difficulty: learning how to talk to physicians and maneuver through the medical thicket, facing cancer as it affected the family unit, and coping with psychological issues. My experience taught me that there are ways physicians can help.

Empowerment and control are crucial issues for most patients facing a crisis, but the entire medical delivery system seems antithetical to these needs. First of all, there is enormous pressure to be a good patient, which seems to mean being submissive, unquestioning, undemanding, uncomplaining, and acting as if one is oblivious to one's own personal catastrophe. Second, medical environments are intimidating; the technical equipment and medical tests conspire to make one feel less able, less knowledgeable, less in control. And third, some physicians have inordinate difficulty sharing power with their patients. I have experienced physicians who become defensive, even hostile, when faced with questions or requests for second opinions.

I am concerned that the pressure cooker environment of medical school gives competitive, science-oriented students little training in coping with their own fears, recognizing their denial systems, or acknowledging their need for omnipotence. Physicians need to learn how to temper their considerable technical skill with compassion and respect for their patients in crisis. Most physicians do learn.

Telling a patient she has cancer is a nasty business at best. I have great sympathy for physicians who are bearers of bad news, but since it does seem to come with the territory, couldn't medical training programs and continuing education address this onerous task? Surely physicians can be helped to better understand their discomfort, their fears for their own mortality, or their wish to flee from a painful scenario.

Many women do not continue to see the physician who makes the initial diagnosis. Does this reflect the displaced anger of "killing the messenger," or does it indicate communication problems? As a patient, I want to say to my physician, "Look me in the eye; don't talk to me with your hand on the examining room door; find time to talk to me after I put my clothes on; acknowledge me as an adult woman, not a breast; don't deny me hope." I believe that a patient's perception of her prognosis can set the emotional stage for coping and ultimate adjustment.

Once communication between physician and patient has

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been established, physicians need to provide patients with informational sources. Their waiting rooms should be overflowing with information about support groups, postmastectomy exercise classes, and cancer risk counseling. I would have been helped greatly by suggestions of books to read or people to talk to—nurse practitioners, cancer counselors, breast clinic personnel, other women who have had cancer. The information is out there. Should each patient have to reinvent the wheel?

Somehow we have to do a better job of creating a partnership between patient and physician. Michael Castleman, editor of *Medical Self-Care* magazine, observed, "It's not enough for doctors to stop playing God. The rest of us must get up off our knees." Granted, there are women who by nature, culture, or age will take a dependent role with their physicians. There is also a growing population of younger women who want to take charge of their bodies, who view physicians as consultants, not as gods or parent figures. I worry about patients who want their medical personnel to be infallible, omnipotent, and omniscient. What a dreadful burden to place on a physician!

Actually, learning one has breast cancer is easy compared to discovering the appalling lack of unanimity regarding treatment. My reaction was something like, "If doctors don't know what to do with me, how am I supposed to know what to do?" It seems that the lumpectomy and radiation versus mastectomy controversy is largely confined to the medical community. Women are often docile about following a surgeon's recommendations and may not realize until after the operation that they really did have a choice.

In California, physicians are required by law to give their patients a four-page document outlining the various surgical options available to women with breast cancer, which implies that patients need to be involved in the decision-making process. I found it difficult, however, to get usable information at a time when I was panic-stricken and pressed to make a decision. My mind closed down. I did not know what questions to ask, nor could I absorb and retain the answers.

Patients would be well served by bringing a family member or friend along to the various appointments and consultations. My husband and I worked out an excellent strategy: I wrote out all the questions before the appointment; he took all the notes on the physicians' responses. An alternative is to record the conversation on a tape recorder, but some physicians, perhaps understandably, seem intimidated by this practice.

I cannot say that I based my decision about treatment on anything other than informed desperation; I did not have the time, knowledge, or fortitude to do otherwise. The surgeon who did the biopsy on my tumor recommended a mastectomy and argued against lumpectomy and radiation. My "second opinion" recommended a lumpectomy. After a week of agonizing indecision, I decided to have a modified radical mastectomy with the second surgeon because I felt safer "going for broke."

One of the difficulties I experienced was simply getting to see or talk to the surgeons in the short time between biopsy and surgery. It was often impossible to get past the secretaries, to get an appointment on short notice, or to arrange for a telephone conversation.

Patients need an ombudsman—someone to help codify the information. Some women are lucky enough to be able to turn to their internist, gynecologist, or, occasionally, a breast clinic for this invaluable assistance. Many have to go it alone. Of course, in the final analysis, the decision is intensely personal and individual.

Decisions about reconstructive operations are equally difficult for patients because there are several operations, all relatively technical. Many women do not realize that breast reconstruction will not produce a "matched set." One friend complained, "I just wish they'd showed me a picture. I didn't even know what a mastectomy would look like!"

In monitoring a patient's recovery, physicians need to remember that a breast cancer patient is a whole human being with her own set of psychological and social responses. Her family is probably profoundly affected by her illness. Yet I recall no physician who asked me how my husband or children were coping with my illness.

I have become acutely aware that many women with breast cancer have to take responsibility for making both family and friends feel okay about the disease. The patient is in the peculiar position of having to prop everybody up until they are strong enough to support her. Family and friends can get pretty shaky when faced with cancer. Under the best of Hollywood circumstances, people accept and acknowledge each other's fears, talk and cry together, keep the communication lines open, and provide endless love and support through thick and thin. Reality is sometimes pretty grim; illness, hospital stays, the financial burden of cancer, and the impact of chemotherapy and radiation treatment are terribly stressful on the whole family.

Often our children are disturbed by our illness, our being in the hospital, our inaccessibility. There are virtually no guidelines available for parents to help them explain cancer to children. There is a lot of information on talking to children about death, but assuming that breast cancer is not a death sentence, how does one explain that to a 4- or a 14-year-old?

My 17-year-old daughter said that being told about my breast cancer felt like a bad dream. "I don't see any way I could have been told about it that would have made it any easier. The word cancer is so scary. Everyone was terrified. I was scared for my mother, for my family. I kept thinking, what if she dies? At night, I remember crying and crying because I felt I couldn't do anything to save her."

I have taken some comfort from the notion that confronting serious illness as a family and developing coping strategies have enhanced my children's survival skills. Our daughter seems to have regained her equilibrium. "It was a very awful time, but you get through it. Mom doesn't have cancer anymore, and I don't see her as fragile but as a very strong person. She's back to normal; we're back to normal."

My biggest psychological adjustment was coping with my fear of dying. There has been a lot of illness and death from breast cancer in my family. It was almost impossible to separate cancer and dying in my mind, no matter how many people reassured me that I was probably going to walk away from this scot-free (I had a small tumor, no lymph node involvement). I felt as if my safety net was torn; never again could I feel entirely safe, entirely protected. The next difficulty was dealing with a different body; first, with only one breast, and then, after my prophylactic mastectomy, discovering what it was like to have no breasts at all. I do not think that breast loss, per se, was an overwhelming issue, but being

a sexual woman without breasts was a painful adjustment. Time, therapy, research, and talking to other women all helped, and each healthy year that passes helps even more.

Women have talked to me about needing more intimacy, tenderness, and reassurance after breast cancer. Both men and women can be equally threatened by the illness as well as by the loss and disfigurement of a mastectomy or quadrantectomy. If breasts were a major source of erotic stimulation for either partner, the impact is considerable.

Many women have used change to put themselves back on track. For some, that has meant counseling, support groups, visualization, or meditation; others have used dietary changes and alternative medical approaches. Some women shed unhappy marriages or take up new careers—they re-evaluate their lives.

Women diagnosed with breast cancer often resolve the crisis through a clarification of values, accompanied by an increased sense of immediacy and a greater appreciation of life. I know that I will never be the same person I was, physically or emotionally. I have found that sadness, depression, and generalized anxiety have given way to a reordering of my priorities and plans for my life. Nietzsche sums it up quite well: "Whatever doesn't kill you makes you stronger."

SUGGESTED READING

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* * *

Alignment

She shaves her legs daily:
She never nicks her knee,
Doesn't miss a patch—
She spills no blood.

In her closet shoes
Are evenly paired, toes out,
None need polishing.

Automatically at tables
She lines up silverware,
The fork perfectly centered
Where the napkin was.

Now we sit on stiff chairs,
A waiting room.
She resists an impulse
To re-align the magazines.
Taut sides of upper arms
Press inward
On presently balanced breasts.

Margaret Kaufman
Kentfield, California

Women and Medicine

Women's Choices—The Ethics of Maternity

ALBERT R. JONSEN, PhD, *Seattle*

In general, both within and without medicine, respect for women's preferences in many spheres of life has not been a notable virtue of western culture. The men of medicine have long distrusted and sometimes disdained the preferences of their women patients. At worst, the choices women made about themselves, their lives, and their health could be put down to that unique female disorder, "the vagrant uterus," from which we have the term "hysteria."[1] At best, their preferences could be discounted as the vagaries of the weak and simple, best overruled by the strong and wise. The title of a 1978 book bears witness: *For Her Own Good—150 Years of Experts' Advice to Women.*[2]

Surely it has not been uncommon for physicians to say no to women patients not because women's preferences were for the impossible or the unethical—although the refusers often pretended so—but because the preferences were those of . . . a woman. In recent decades, respect for the autonomy of a patient has become an accepted ethical principle in medicine. It has replaced, in theory at least, the long revered paternalism of medicine that permitted physicians to go about their duties "calmly and adroitly, concealing most things from the patient."[3] Now, physicians must not only inform fully and obtain voluntary consent to the recommended procedures but also respect the preferences of patients, even if they refuse the physicians' recommendations. Clearly this new principle of ethics is intended to apply to men and women patients alike.

Attitudes, principles, and practices, however, are often difficult to reconcile. Despite educational efforts, the sexism that ranks the intelligence, emotional stability, and plain common sense of one sex over the other still continues to taint the attitudes of physicians toward their patients. This includes, of course, women physicians, who grew up with or were taught the same attitudes toward women as their male colleagues. Recently, a new set of problems concerning the preferences of women patients has arisen. Like so many of the ethical problems of modern medicine, these new issues are created by technologic advances. Like the old attitudes, these problems involve a discounting of women's preferences. Unlike the old problems, they are not simply paternalistic or sexist—although they, too, may be tainted with these prejudices.

This new set of problems, like the ethical issue of abortion, involves the preferences of women toward their fetuses, but the more recent issues add a new twist. Abortion is, in a sense, the most straightforward of these problems. It asks quite directly, "Does a woman have the moral authority to empty her womb of the developing product of conception?" The answer will be, quite directly, "yes," if that product is considered to be, in some substantive way, less than an independent and full human being. It will be "no" if, by reasoning, intuition, or faith, that product is claimed to be equal to the mother in human status and importance. The case itself is simple; the controversy lies in the complexities and multiple interpretations of the "if" clauses.

The new issues are complex even in their initial formulation. They all involve decisions in which the nature and status of the fetus are not in doubt. With each of these issues, the decision involves the birth and subsequent disposition of a life rather than its termination. Three recent cases will make my point: a pregnant woman's refusal of therapy recommended for her fetus; a woman's desire to donate the organs or tissue from a fetus or infant she has conceived or borne; and a woman's contractual agreement to provide a womb for the gestation of an infant engendered, in whole or in part, by other persons and to be transferred to them after birth.

These cases all involve a decision made before or during pregnancy but bear on the welfare or status of a born infant. Thus, the controversy of abortion is eliminated; there is no doubt that a human being—and a person under the law—will be affected by the decision. The decisions are occasioned by the availability of modern technologies that can make diagnoses and offer prognoses and even therapy for the fetus in utero, or, in the case of surrogacy, facilitate the conjunction and transfer of gametes and embryos in various ways. Thus, we have new problems bearing the marks of modernity: technologic virtuosity facing the limits of human autonomy. The question is, "Ought we to do what we are capable of doing?" or, more directly for the thesis of this essay, "Can or should physicians say no to women who express preferences of this sort?"

The first question is the more general one, suitable in every sort of ethical problem. It takes on a feminist tone in these three cases because the "we" always involves a woman and the question is whether the mother has moral authority or whether her autonomy to make decisions should be limited in certain ways. It is in this respect something like the old problem of abortion: the decision is being made while or before the product of conception is within her body. The claim can be made that the fetus is in some morally important way hers, with the implication that it is hers to dispose of as she wishes. The difference lies in the fact that a baby will be

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born—unless it dies in utero as a result of her decision to refuse therapy—and, so, exists in its own right and as the object of society's interest.

We are forced to ask whether women's decisions and preferences in cases such as these should be respected or whether they should be restricted by moral disapproval or even by law. The spectre of medicine's ancient sexism may hover over these cases, but the issues are more complex. The first complexity is that these cases are issues not only of women's choices but also of mothers' choices. They all involve the ethics of maternity.

Being a parent is a matter of high moral seriousness. From ancient times, mothers in particular have been held to have certain responsibilities toward their offspring: they must cherish, nourish, protect, educate, and, eventually, relinquish them into the wider world. Carrying out these responsibilities entails self-sacrifice that is sometimes heavy. In return, maternal sacrifice theoretically gives rise to filial duties of respect, love, gratitude, and eventual support. Rooted in instinct, these activities are reinforced as values. While they vary in definition and extent in various cultures, they are inextricably tied to being a mother; failure to fulfill them brings blame and, occasionally, repudiation. There is, then, a complex ethic of maternity, an ethic that pertains only to women.

Curiously, there is a question about when a woman becomes a mother. Does maternity begin with conception and continue through pregnancy, or does it begin only with the birth of a child? While the answer is debatable, it can be argued that maternity, properly speaking, begins only at the point where the various duties of maternity can be exercised by the voluntary choices of the mother. This implies that birth initiates maternity. There is now an infant who can be mothered. This also implies that during pregnancy, the duties of maternity do not yet exist and, consequently, the pregnant woman is not a mother. From this viewpoint—admittedly debatable—the ethics of maternal duty do not apply to the decision to abort. Maternal duties do exist prospectively, however, in those situations when maternal decisions affect the child intended to be carried to term. In general, we summarize the maternal ethic by saying that the mother and, prospectively, the pregnant woman must make decisions that are "in the interest" or "in view of the welfare" of the child.

This somewhat dense argument is necessary if we are to understand the ethical problem posed by these three examples. It suggests that a woman's decisions while pregnant differ radically, depending on whether the fetus will or will not be carried to term. The ethics of those decisions that lead to the preterm death of a fetus—namely, its abortion—are radically different from the ethics of decisions about the fetus that will come to term as an infant.[4]

Maternal Refusal of Therapy for Fetal Indications

This issue has been reviewed recently in several articles.[5,6] A commonly discussed but infrequent situation is one in which signs of fetal distress have led an obstetrician to recommend immediate delivery by cesarean section and the mother has refused the operation. A less typical though perhaps more frequent situation would be a mother's refusal to comply with recommended treatment of diabetes or phenylketonuria or to abandon certain habits, such as smoking or drinking, that may be deleterious to the health of her fetus. In these cases, the fetus will come to term unless the failure to provide the recommended therapy leads to its death, but it may be born with damages that therapy might have averted.

Obstetricians seem to be very reluctant to tolerate maternal refusals of this sort.[6] On the other hand, ethicists and lawyers seem to respect maternal refusal, even when it puts the fetus at great risk.[5] The opinion of the Ethics Committee of the American College of Obstetricians and Gynecologists follows the ethicists and lawyers, with slight concession to the practitioners' inclination: "Every reasonable effort should be made to protect the fetus, but the pregnant woman's autonomy should be respected."[7] The distinction between the legal and the ethical is important. The maternal ethic of choosing in view of the infant's welfare is already in effect. The child, whose life may be irreparably damaged by the woman's preferences, does make a prospective claim on her. The ethics of maternity require a sacrifice of self (although not a self-destructive sacrifice) so that the child may live as well as possible. The law, on the other hand, may—and on the analysis of some constitutional lawyers must—treat the maternal decision as a private matter.

The ethical judgment in the matter of a pregnant woman's refusal of a treatment that, although it may pose some risk to herself, might benefit her infant, is rather clear. The ethics of maternity require both a determination to act with a view to the welfare of one's child and a degree of self-sacrifice in order to attain that welfare. A woman is judged morally reprehensible if she is aware of a risk to her fetus and future infant and of a remedy for that risk and refuses to take it. Naturally, there may be questions about her comprehension of risks, her freedom to avoid them, and the efficacy of the proposed remedy.

The delicate matter, however, is whether to say no to the preferences of such a woman. In these cases, saying no could take two forms: coercion or withdrawal from caring for the patient. Neither is justifiable. Coercion, a vigorous attack on another's physical or psychological integrity, must be justified by a high assurance that the value one hopes to protect—in this case, the infant's health—will be protected. Even in the most obvious situations, such as monitored fetal distress, this is questionable. Withdrawal of care seems to be an act of frustration and may abandon the future infant to an even worse fate than it might suffer if attended with patience. Thus, the physician is placed in the troubling situation of saying, "No, this is not right" but saying, "Yes, I will continue to do my best to help you and your baby under the immoral conditions you impose upon me."

Maternal Donation of Infant Organs

A pregnant woman's intention to donate organs or tissue from her fetus or infant is a less clear case than refusing therapy recommended for her fetus. There can be several versions. In one, the diagnosis of anencephaly in utero may prompt the mother to donate the organs of her infant who is faced with impending and certain death. In another version, a woman who is about to have an abortion consents to the use of neural tissue taken from the abortus for transplantation. In a third version, a woman decides to conceive in order to abort and donate tissue to a relative in need of transplantation. These three versions must be judged differently.

In the first, the mother knows she can do nothing to save the life of her infant. In the face of inevitable death, the donation of organs that will give life to another infant is the most the mother can do. Her child's welfare consists of being

the source of good for another after its own short life is over. A woman who gives her consent to the use of the aborted tissue neither benefits nor harms her future infant; it will never come to term. Indeed, one might argue that she has no authority to consent at all, having given up all interest in the fetus by her decision to abort.[8] The final case, conceiving in order to donate, is manifestly unethical. It engenders human life only in order to destroy it. All of the imperatives of maternal ethics are contravened; even abortion, which in the most liberal ethical form permits a woman to choose to empty her uterus, is justified by the claim that continuing the pregnancy in some way harms her.

Thus, these three versions call for three different moral answers. In the first, the physician's answer can be, "Yes, I will cooperate with your donation of your infant's organs after its tragic death." In the second, the physician may say yes or no, depending on his or her view of the reason why the tissue becomes available, namely, abortion. In the third, the answer must be, "No, I cannot cooperate with your intent to conceive in order to destroy, even with the intent to save another."

Surrogacy

The final case, commonly called surrogacy, involves the gestation of a fetus that has been engendered either totally or in part by other persons. Here, the infant will be born, it is hoped, healthy and transferred to the party or parties who provided gametes. The woman who has borne it will not be its mother in the sense described above; she will not bear the responsibilities of mothering. In one sense, this practice appears to be similar to adoption: the woman who engenders and bears gives up custody of the infant after birth—sometimes even by an agreement before birth. Yet, in the form of surrogacy, the practice has aroused most vigorous debate. One of the questions in that debate asks whether a woman has the moral right to enter into a surrogacy agreement. Those who answer no impose a limitation of a woman's preferences. They may or may not suggest that this moral restriction be sanctioned by the law.

Surrogacy poses a peculiar problem for the ethics of maternity: whether a woman may ethically undertake conception and gestation with the intention aforethought of not accepting the ethic of maternity. The woman who bears a child and puts it up for adoption does not conceive with motherhood in mind.

Our society is uncertain about this issue. Saying yes or no is surrounded by hesitations, doubts, and qualifications. There is little evidence on either side. Serious questions about the effect of the practice on important social conventions—such as the social identity of the child, racial and religious heritage, inheritance, genetic pedigree—are as yet unanswered. Questions about the potential for exploitation of women and about equity among social classes are still unclear. When such uncertainty prevails, a yes or no answer is equally justified. The ethical discussion must continue and not be put aside as a minor moral snag in the inevitable progress of technology or as a puritanical obstruction to a woman's wishes to help herself or another. It may well happen that the arguments tip toward the negative and that surrogacy will become a practice to which physicians should say, "No, I cannot cooperate."

The point of this essay is to show that new reproductive science and technology create problems that directly challenge the autonomy of women. At the same time, the challenges do not come from their traditional sources, namely, the sexist view that women's decisions are defective simply because they are women's. The challenges come from the new capability to make decisions about one's offspring on the basis of information gained during pregnancy or to manipulate the reproductive processes.

In some of these cases, the autonomy of a mother's choices should be respected because they do not violate the principle of the ethics of maternity, namely, benefit of the child and self-sacrifice of the mother. In other cases, one or another of these principles is directly or indirectly violated. Finally, in some cases, the moral arguments remain indeterminate. As always in moral discussion, principles, circumstances, motives, and consequences must be continually reviewed. The ethics of maternity and of obstetrics are an amalgam of ancient values and new possibilities and, as such, call for reflection by patients, the public, and the medical profession.

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I hate
This wretched willow soul of mine
Patiently enduring, plaited or twisted
By other hands.

Karin Boye (1900-1941)
Swedish Poet

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Taking Care of Patients—Does It Matter Whether the Physician Is a Woman?

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Researchers have recently begun to compare male and female physicians' attitudes toward patients, medical knowledge, and practice styles. Although women start medical school with more "humanistic views," the conservative effect of medical socialization on both male and female students attenuates these differences. While some studies suggested that men are more scientifically knowledgeable, recent studies showed no significant differences in physicians' medical knowledge. Male and female physicians also had comparable diagnostic and therapeutic behavior. In the intimate world of physicians and patients, however, there were notable differences. Women physicians seemed better able to communicate sensitivity and caring to patients, which may account for the common perception that women are more caring and empathic physicians. Medical educators may wish to study more closely female physicians' communication styles to identify these behaviors and inculcate them into all physicians.

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What are the implications for patients of the recent increase in the number of women physicians? Science and technology, the cornerstones of 20th century medical care, are stereotypically associated in our society with masculinity.[1] Critics accuse medicine of overemphasizing these masculine ideals and deemphasizing the traditionally feminine values of nurturing, empathy, and sympathy. Such a bias is thought to be responsible for many of the ills currently confronting the medical system: structural incentives that encourage technologic development over physician-patient interactions; physicians who are technically superior but interpersonally inadequate; and patients who, although living longer, express greater dissatisfaction with the medical care system.[2-4]

Many think that the influx of women physicians will lead to a greater emphasis on caring and nurturing and that this will improve patient care. Now that women constitute a third of entering medical students and roughly a sixth of all physicians, it is time to critically evaluate whether the sex of a physician influences patient care. We will review the literature regarding women physicians' practice, with special emphasis on their diagnostic, therapeutic, and interpersonal skills.*

Unfortunately, the data in this area are sparse. While there is a growing literature comparing male and female physicians in some specialties, there are little data comparing them in others. Moreover, methodologic flaws in data collection and analysis limit our ability to make definitive statements regarding the effect of the sex of a physician on patient care. For example, many of the studies attempted to evaluate male and female physicians' "humanism" but did not adequately define the term. One is thus not sure what the respondents were assessing.[5] Furthermore, important confounding variables, such as a patient's age, sex, and illness, were not controlled for in most of these studies. We can thus provide only preliminary data concerning the importance of a physician's sex in patient care.

There is little question that male and female physicians

*We realize that women physicians do not constitute a homogeneous group (nor do male physicians). It is thus more accurate to say that this article discusses "average" male and female physicians. It may well be that intragroup variation is more important than the differences between male and female physicians. Further research needs to be done in this area.

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are perceived as having different practice styles. Medical students, for example, reported female attending physicians were more sensitive and less egotistic than male attending physicians.[6] Nurses said women physicians are more "humanistic" and have greater skill in communicating with patients.[7] When asked, attending physicians also rated women residents as "more humanistic" than male residents.[8,9] Recently, investigators have analyzed the relationship between a patient's satisfaction and the physician's sex. A study at the University of California, Los Angeles, found that patients who had seen a female resident reported significantly higher total satisfaction scores than patients who had seen a male resident. Women residents also scored higher on a measure of physicians' manner and interpersonal style. This was true for both male and female patients.[10]

This increased satisfaction with female physicians is particularly pronounced among female patients. Comstock and colleagues found that female patients seeing female internists expressed greater satisfaction with their care than any other gender mix of physicians and patients.[11] Women also described female obstetricians as more empathic and more interested in them as human beings than male obstetricians.[12] Finally, there is a growing body of data showing that patients are more comfortable talking with a physician of the same sex.[13] For example, numerous studies have shown that, if given an option, female patients are more likely to see a female than a male physician.[14,15]

The finding that patients are more satisfied with women physicians' care, although tentative and requiring further confirmation, raises important questions for medical educators. Is this increased satisfaction with women physicians merely a reflection of prevalent social assumptions that women are more nurturing and caring than men? Or do women physicians actually care for patients differently? If satisfaction is related to women physicians' different practice style, medical educators should identify those attitudes or behaviors that result in increased patient satisfaction and inculcate them in all medical students.

To determine why patients perceive female physicians differently, we examined studies on differences between male and female physicians' medical knowledge; data on whether female physicians' attitudes toward patients differ from their male counterparts; and research on sex differences in physicians' behavior.

Physician Knowledge

The belief that men are more scientifically knowledgeable and technologically competent than women is still prevalent in our society, but there is no evidence that men and women physicians emerge from their training with a different knowledge base. During medical school, there appears to be little difference in the academic performance of male and female students. In the early 1970s, women had a higher dropout rate than men—15% versus 10%—but this increase was due to the higher number of female students who left for personal reasons.[16] The current rate of academic attrition among female students is not significantly different from their male counterparts.[17] Although studies showed women's performance on standardized tests (National Board Examination Part I and on schools' comprehensive examinations) in the first two years of medical school was slightly lower than that of men, their scores in the last two years (National Board Examination Part 2), as well as their clinical evaluations, were not significantly different.[18-20]

Recently, investigators have begun to look closely at performance by sex during residency training. The best studies have been conducted by the American Board of Internal Medicine.[8,21] Attending physicians subjectively rated male residents higher for medical knowledge and technical proficiency, though women received higher ranks for humanistic attributes. Women were also less likely to pass the written certification examination than were men, although this difference has narrowed substantially over the past 15 years. In 1973, only 59% of women passed the test (compared with 76% of men), while in 1986, 80% of women passed (compared with 86% of men). A national study of psychiatric residency program directors' evaluations also found that attending physicians thought male residents had superior knowledge and patient management skills. The authors hypothesized that this difference was due to sexism rather than objective findings of differences in knowledge.[9] In contrast, in a study of surgical residents, women exhibited superior academic performance.[22]

Available data from the other specialties, although sparse, showed little or no sex differences in knowledge. A recent report from the American Board of Pediatrics documented no difference in the scores or pass rates between male and female residents.[23] A study of board scores from a family practice residency program confirmed this finding.[24]

Unfortunately, none of these studies considered the evaluators' biases. In the sociologic literature, there is evidence that an evaluator's assessment is influenced by a student's sex. Information regarding the sex of the evaluators and their general attitudes toward women would be helpful in delineating whether attending physicians think of women in stereotypic ways, thereby leading to biased evaluations of women physicians' knowledge.

There are conflicting data regarding whether women physicians' medical knowledge differs from that of their male counterparts. If there are differences, they are small and appear to be narrowing. It is difficult to know whether these small differences are clinically important in patient management. There are little data, to our knowledge, that relate physicians' scores or ratings to objective medical outcomes or patient satisfaction.

Physicians' Attitudes Toward Patients

Much of the data examining physicians' attitudes toward patients are derived from studies of medical students during the late 1960s and early 1970s. Psychometric studies showed that women medical students rated themselves higher on sensitivity to relationships, acceptance of feelings, and alertness to moral and ethical issues.[25] These studies also showed that women students considered themselves more patient-oriented and placed a higher value on patient contact.[26-28] A more recent study found fewer sex differences, however, possibly because more women are attending medical school and because changes in the social environment allow women to adopt less stereotypically feminine roles.[29]

There are also recent data suggesting that the differences between male and female students' attitudes attenuated as they progressed through medical school.[30,31] In the only longitudinal study reported in the literature, Leserman interviewed 275 medical students during their freshman and se-

nior years concerning their attitudes toward patients, the medical profession, and feminist issues. Initially, female students were more oriented toward the "humane side of medicine." Over the four years of medical school, both male and female students became less concerned with the "humane" side of medicine. Because similar conservative changes occurred in both groups, most of the sex differences that appeared in the first year persisted into the students' senior year.[32]

The sparse data dealing with practicing physicians' attitudes toward patients show few differences between male and female physicians' attitudes. Women physicians' assessments of the type of patients they enjoyed or disliked were no different from those of male physicians.[33,34] Male and female physicians also responded similarly concerning how they assessed the authenticity, truthfulness, and emotionality of their patients.[35] One exception should be noted. Women medical students and physicians were more sensitive to issues regarding sex discrimination, contraception, and appropriate health care for women. Moreover, their sensitivity to these issues remained high and, over time, continued to differ significantly from that of their male counterparts.[35-38]

There is no clear answer to the question of whether female physicians have different attitudes from male physicians toward their patients. Earlier in their training, women may be more concerned with the psychosocial aspects of patient care and place a higher value on patient contact. Data suggest, however, that as women progress through medical school into residency training and then into practice, their attitudes become less distinguishable from those of their male colleagues. This tendency of both male and female students to become less concerned with the psychosocial aspects of care is troubling and requires further study. The difference between male and female medical students' knowledge and attitudes, however, appears insufficient to explain the widespread perception that men and women physicians practice differently.

Physician Behavior

Perhaps the most important and least studied area deals with the relationship between the sex of physicians and their actual behavior with patients. Although the data appear contradictory, a coherent theme is discernible: while there is little difference between men and women physicians' diagnostic or therapeutic behavior, there is a difference in the way they communicate with patients.

Most of the available information on sex differences is from analyses of "hard" data such as the number of specific treatments offered or patients' morbidity and mortality. Although flawed—not controlling for such basic variables as the number of years in practice or patient characteristics—the available information reveals few important differences in diagnostic or therapeutic practices. The National Ambulatory Care Medical Survey of approximately 3,000 practicing physicians supplies excellent data regarding physicians' daily practice. This study showed many more similarities than differences in the diagnostic and therapeutic behavior of male and female internists, pediatricians, obstetricians/gynecologists, and family practice physicians. What differences were apparent in the survey were small and may be related to different patient populations. For example, a larger percentage of young patients making their initial visits to physicians saw women physicians. This may explain why women practitioners did preventive tests such as Papanicolaou smears or blood pressure checks more frequently.[39-44]

Other studies confirmed the absence of significant differences in clinical behavior.[44,45] Greer and co-workers asked family practice physicians to describe how they would work up a variety of common complaints, such as headache and fatigue, and found no significant differences between physicians' suggested workup based on their sex.[45] A national study of psychiatrists also showed no significant differences between male and female physicians' diagnoses, prescribing of psychotropic medications, or rates of admitting patients to hospital.[46]

Based on women physicians' attitudes toward "women's issues," significant differences between male and female obstetricians' practices might be expected. There is a great deal of anecdotal evidence that women obstetricians have different treatment patterns from those of their male colleagues.[47] Cartwright and Waite found that women physicians were more likely to consider alternative methods of birth control for those women who were concerned about the side effects of birth control pills.[48] Other data sources, however, such as the National Ambulatory Care Survey, reported only modest differences between the practices of male and female obstetricians.[40,44]

Given prevalent social stereotypes of women, women might be expected to be more understanding of patients' psychosocial problems. Surprisingly, a variety of studies that attempted to analyze physicians' behavior have failed to show a significant difference between male and female physicians. Women physicians seemed no more likely to detect or record patients' psychological, social, or sexual problems.[49] Similarly, studies that analyzed physicians' caring behaviors reported no difference between men and women physicians.[11,50]

Communication Style

How can we reconcile the claim that female physicians are more caring when data show that male and female physicians' behaviors are similar? Perhaps patients' perceptions of female physicians as more sympathetic are a result of their stereotypic views regarding women. Patients, expecting women physicians to be more empathic or nurturing, respond based on these expectations. An alternative explanation for the lack of differences found in these studies is that the research methods used were inadequate to delineate subtle differences that do exist. Recently, a group of researchers argued that a closer investigation of the actual discussion between physicians and patients is necessary to understand medical care.[51] Perhaps analyzing the physician-patient interview can explain why patients perceive women physicians as more "humanistic."

One reason to hypothesize that women physicians communicate differently with patients is that, like other women in our society, they have been socialized to accept a less directed, interactive style of communication. Women's style of speech is typically characterized by less obtrusiveness, as exemplified by less speech intensity and a more frequent use of hedges and euphemisms. In mixed conversation, men, not women, are more likely to decide the topics of conversations and to dominate the process of turn-taking.[52]

In medical school, physicians are socialized to be assertive. Communication between physicians and patients uses directed questions and emphatic speech to control both the

flow and the topic of conversation. Asymmetry in conversational style is further emphasized by the frequency with which physicians ignore patients' questions or refer to patients by their first name.[53]

Women physicians thus have been influenced by two very different models of interaction. The question is how they integrate these two models of communication into their clinical practice. Might this account for the difference in patients' perception?

Hints that something different might be occurring in the interaction between patients and women physicians are found in the National Ambulatory Care Survey data. In a trend that is relatively consistent across specialties, women physicians were found to spend more time with their patients (17 minutes per visit versus 13 minutes per visit) and a greater proportion of visits lasted 16 minutes or longer (for internists, 55% versus 38%). These data also showed that women internists were more likely to engage in therapeutic listening and counseling.[40-44]

More powerful evidence that women and men physicians interact differently with patients and that this behavior accounts for patients' perception of women physicians as more caring comes from recent studies of physician-patient communication. In pediatrics, there is preliminary evidence that women communicated differently and that this accounted for patients' perceptions of women physicians as more compassionate.[54] Wasserman and associates videotaped 40 initial visits to a pediatric clinic in Seattle. Coders found that the four women physicians in the study were more empathic than their five male counterparts and that this increase in empathy accounted for mothers' increased satisfaction with women pediatricians.[55]

A study of internal medicine residents in New York City reached similar conclusions. Women physicians were rated by observers to be more egalitarian in their relationship with patients. For example, male physicians raised 67% of all the issues discussed while female physicians raised only 59% of the topics. Patients who saw women physicians were more likely to raise issues that were of concern to them. Coders also found women physicians were more respectful of their patients' concerns and more responsive to psychosocial issues.[56]

Another expression of physicians' different communication styles can be found in West's linguistic microanalysis of physician-patient communication. Male physicians interrupted their patients more frequently, and West thought this style was used as a means of control. Women, on the other hand, interrupted their patients no more than they were interrupted. This lack of controlling behavior may be one reason why previous researchers have found women physicians to be more respectful of their patients' concerns and more egalitarian in their relationships.[57,58]

Conclusion

Recent data suggest that in the intimate world of physicians and patients, there are important differences between men and women physicians. While the technical skill of physicians does not seem to differ, women physicians seem better able to communicate sensitivity and caring to patients. Women's tendency to listen without interrupting and to allow patients to present their agendas may produce stronger rapport by providing patients more time for discussion. These skills in communication may account for patients' perceptions of female physicians as more sympathetic and caring.

The potential benefits of these aspects of female physicians' communication style are immense. Excellent interviewers obtain substantially more information from patients than poor ones.[59] Moreover, recent research has shown a positive relationship between patient satisfaction and patients' compliance with their therapeutic regimens.[60] These findings suggest that better physician-patient relationships might lead to improved patient care.

Further research is needed on the effect of both the physicians' and patients' sex—and their interaction—on the physician-patient relationship. Do the differences between men and women physicians, for example, cut across specialties or are they limited to only one or two specialties? More research is also needed to better describe the factors that cause patients to describe women physicians as more empathic. Further study of the differences between men and women physicians' nonverbal styles of communication might also prove insightful. Finally, we need to determine how and if these behaviors can be taught to all students.

The answers to these questions hold the potential to improve all physicians' abilities to communicate with patients. Medical educators need to carefully study medical communication to determine the most effective way to improve students' ability to interact sensitively with patients. The challenge confronting medicine in the coming decades is to learn from women physicians how to better integrate the art and science of medicine in order to improve patient satisfaction and care.

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* * *

What I Want in My Physician

As a post-menopausal woman with experience as the patient of excellent doctors, I know what I want from you.

Excellent credentials, experience, reputation, and attitude. Whenever possible, I choose the personal physicians of other physicians and their families; this way, I know I am getting superb care. I do not mind paying more for a fine physician because I believe in financial reward for excellence. I will feel better about our relationship, however, if I know your real reward comes from healing your patients rather than from building your stock portfolio.

Absolute trust and respect. This must work both ways. Please take me seriously. Don't scoff at my fears or odd symptoms. Because I want to trust you to work with and for me, I will follow your advice and keep you informed when something you recommend does not seem to be working well. I want the truth—always—and will always tell you the truth.

Effective use of our time. I do not want to be kept waiting for more than 20 minutes. I am busy too; when I am kept waiting, others who may be waiting for me are inconvenienced. If there are always half-hour to hour delays in your office, I may stop being your patient.

Your undivided attention. Do not be distracted, evasive, or bored when I am in your examining room or office. I come to you because you know things I do not but do not try to talk me out of my symptoms. Do not prescribe drugs, treatments, or operative procedures I do not need, please find out what other drugs I may be taking, do not assume I know what I should not eat or drink with a drug you prescribe, and tell me about the possible side effects.

—CAROL MINDEY

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Women and Medicine

Occupational Mortality of California Women, 1979-1981

GWENDOLYN DOEBBERT, MA, MS; KATHRYN R. RIEDMILLER; *and* KENNETH W. KIZER, MD, MPH, *Sacramento, California*

A review of California's mortality data for 1979 through 1981, encompassing 61,561 female and 111,877 male deaths, shows differential female mortality risks by labor force status and by occupation. High patterns of risk were found for women in a number of occupations, including waitresses, licensed vocational nurses and health aides, cosmetologists, telephone operators, housekeepers and janitors, and launderers and dry cleaners. Patterns of mortality risk were similar for each race within these occupational groups. The mortality risks for women were generally higher than those for men. The association of mortality with certain occupations does not necessarily imply a causal relationship but is certainly a signal that further research is required and that physicians need to consider work-related factors in evaluating the health of women.

(Doebbert G, Riedmiller KR, Kizer KW: Occupational mortality of California women, 1979-1981, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:734-740)

Recent increases in the female work force have raised important questions about the health effects of this societal change. The percentage of women in the US and California labor force increased by a third between 1960 and 1980, rising from 38% to 52%.[1] By 1987, 56% of women in the United States were in the work force.[2] The comparable figures for women with children younger than 6 years and for women with children aged 6 to 17 years were 57% and 72%, respectively.[3] These demographic changes in the work force have resulted in increased exposure of women to potential occupational hazards.

Studies investigating the health of working women were practically nonexistent until this decade. Earlier studies of occupation and mortality, including the 1959-1961 California study and the 1969-1971 Washington State study, were limited to white men.[4-8] The relatively few studies currently available on women's occupational health offer seemingly contradictory and fragmented data and emphasize the lack of information about the impact of specific occupations on women's health.[9-16]

Current data indicate strong associations between a woman's work and her physical health.[17-22] While a "safer" nature of women's work has been presumed, it has not been shown.[13,23] Indeed, occupational health risks vary greatly among women, as they do among men. Unfortunately, most studies that compare health risks among women by occupation or industry have looked only at a limited number of occupations, or at one occupation in comparison to a control group. Few studies have compared occupational mortality by race and between sexes.[8,11,23-27]

The California Occupational Mortality Study, 1979 to 1981 (COMS), provides the first extensive data base of mortality information for California women, as well as for men, by race and detailed occupation and industry categories.[28] This COMS data base enables female mortality and comparable mortality data for men to be analyzed by various occupation, industry, and cause-of-death groupings.

Methods and Materials

The methodology of the California Occupational Mortality Study has been reported in detail elsewhere.[28] In brief, COMS information was obtained from two sources. First, California death certificates for all decedents, ages 16 to 64 years, were the source of age, sex, race—white, black, Asian—usual occupation, usual industry, and cause of death data. The occupation and industry items on 173,438 death records (61,561 women; 111,877 men) were coded for the COMS, using the same procedures employed by the US Bureau of the Census. The cause of death was coded according to the International Classification of Diseases, Ninth Revision.[29] The second data source was estimates of California's working population by age, sex, race, occupation, and industry generated by the US Bureau of the Census from the 20% sample of the 1980 California census.

Census-based standardized mortality ratios (SMRs) and 95% confidence interval estimates were calculated as shown in Table 1. SMRs by occupation were age-adjusted and presented by race. Industry SMRs were age- and race-adjusted. SMRs with interval estimates ranging entirely above 100 were defined as indicating a significantly increased risk of death compared with the standard population subset and are referred to as "highs" in this article. A comparable standard determined significant "lows." Significant SMRs were limited to those with at least 6 deaths by cause and with at least 51 deaths for the occupation or industry group. SMRs with interval estimates ranging 90 or above were defined as elevated or "marginal" for this study.

From the Health Demographics Section, Health Data and Statistics Branch (Ms Doebbert and Ms Riedmiller), California Department of Health Services, Sacramento. Dr Kizer is Director of the Department of Health Services.

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ABBREVIATIONS USED IN TEXT

COMS = California Occupational Mortality Study
LVN = licensed vocational nurse
SMR = standardized mortality ratio

Results

The COMS data show notable differences in the risk of premature mortality by occupation for California women. In Figure 1, SMRs are presented for women by race in six summary occupational groups. High SMRs were found for both white and black female service occupations and for operators, fabricators, and laborers. For Asian women, only the SMR for managerial and professional specialties was high.

Service occupations, which include traditional female occupations, were associated with the largest number of female deaths, the highest SMRs for all causes of death, and the largest number of high SMRs for the leading causes of death. Between 1972 and 1980, more than 29% of California job growth was in the service area, while service jobs accounted for more than 41% of all job growth between 1980 and 1987.* This trend is projected to continue.[30,31]

Occupational mortality by race for six service occupations—waitresses, licensed vocational nurses and health aides, cosmetologists, telephone operators, housekeepers and janitors, and launderers and dry cleaners—are presented here. Likewise, male and female mortality comparisons for selected service occupations and related industries are discussed.

Leading Causes of Death for Labor Force Women in California

The rank and percent of deaths by selected leading causes of premature death for California women in the labor force—also referred to here as "working women"—and those not in the labor force, aged 16 to 64 years, for 1979 to 1981 are summarized in Table 2. Breast cancer was the leading cause of death for working women in California during the study period, and ischemic heart disease was second. The latter was the leading cause for black women in the labor force. Lung cancer was the third leading cause of premature death for women both in and out of the labor force. Cancer of the digestive organs was the leading cause for Asian working women and fourth for all women.

*Calculated from current California wage and salary employment data from the California Employment Development Department.

Motor vehicle traffic accidents was the fifth leading cause of death for working women. Cirrhosis, which was the fifth cause of death for non-labor force women, was eighth for California working women. Suicide, the ninth leading cause of death for working women, was the eleventh cause for non-labor force decedents. Homicide was the third leading cause of death for black working women (Table 2).

High Mortality Risk Among Women in Service Occupations

Among white labor force women, as shown in Table 3, waitresses had the greatest age-adjusted risk of mortality with an "all causes of death" SMR of 247; this is 2½ times

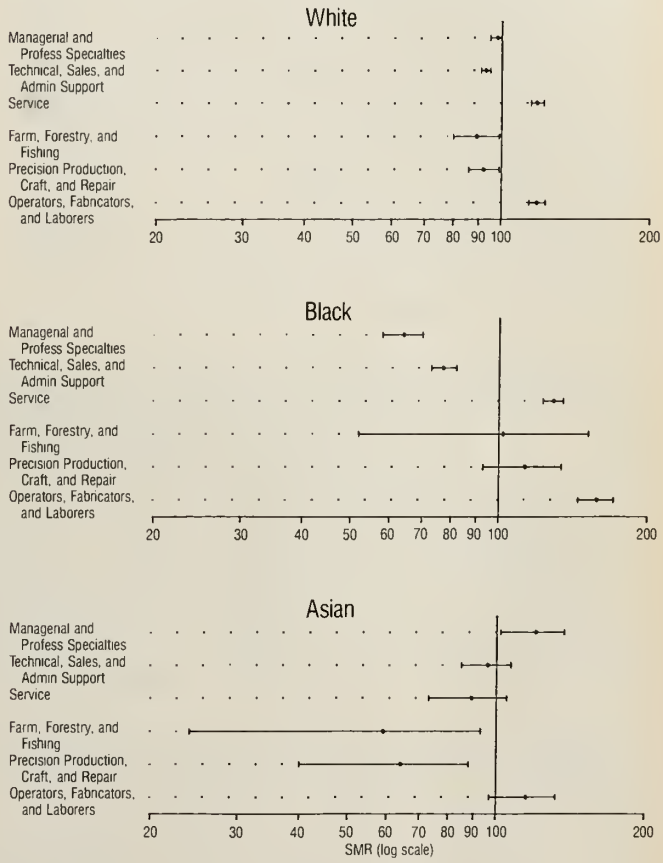

Figure 1.—The graphs show female standardized mortality ratios (SMRs) by race and six summary occupational groups—US Department of Commerce's index—for California, 1979 to 1981 (from State of California, Department of Health Services, Health Data and Statistics Branch, Occupational Mortality Study File).

TABLE 1.—*Computation of Standardized Mortality Ratio, Age-Adjusted by Race, for Ischemic Heart Disease in Female Health Aides, California, 1979-1981*†*

			Ischemic Heart Disease		
Race	*Age, years*	*Population of Female Health Aides*	*Death Rate (3 years/100,000) for All White Women in This Study*	*Expected Deaths (3 years) for Female Health Aides*	*Observed Deaths (3 years) for Female Health Aides*
		(1)	(2)	(3)=(1)×(2)	(4)
White . . .	16-44	85,122	5.59	4.76	14
	45-54	18,607	94.40	17.56	30
	55-59	8,282	299.20	24.78	49
	60-64	5,698	790.19	45.02	92
White Total	16-64			92.12	185

*From California Occupational Mortality 1979-1981.[28]
†White standardized mortality ratio = $(185/92.12)^{1/2} \times 100 = 201$; standard error = $100 \times 185/(92.12 \times 92.12) = 15$.

the expected mortality risk. Three other white female occupational groups had more than 1½ times the expected risk of death: telephone operators, licensed vocational nurses (LVNs) and health aides, and cosmetologists.

Black female launderers and dry cleaners showed a risk of mortality more than three times expected, and black waitresses and cosmetologists had a risk of death about twice that expected. Black female housekeepers and janitors had high mortality, while the mortality risk for white women in this occupational group was about 30% lower than expected (Table 3). An insufficient number of deaths precluded calculating SMRs for Asians in these occupations.

White LVNs and health aides showed high SMRs for 14 of the 15 leading causes of death examined (Figure 2). Both white and black women in this occupational group were at the greatest risk of death from suicide, with SMRs of 245 and 259, respectively. For white women, this SMR is the highest suicide rate found among any of the female occupational groups analyzed. This group showed the only high SMR for suicide among black women (Table 3).

White waitresses during 1979-1981 were at the greatest risk of fatal respiratory tract disease (SMR=430) as shown in Figure 2. Black waitresses showed more than five times the expected risk of death from cirrhosis (Table 3).

The SMRs for all causes of death for white and black female cosmetologists were 168 and 195, respectively. Other accidents, cirrhosis, and ischemic heart disease presented the greatest risks for cosmetologists (Table 3).

The COMS data show a dramatic difference in the mortality risk for black and white female housekeepers and janitors (Table 3). Blacks showed an all-cause SMR of 138, while whites had a significantly low SMR (69) for all causes and no high SMRs. The greatest risk of death for black female housekeepers and janitors was homicide (SMR=171), as presented in Figure 2. Also, this figure shows several extraordinarily high SMRs for black female launderers and dry cleaners, including cirrhosis (SMR=626).

Female and Male SMRs for Selected Occupations and Industries

Female and male SMRs for all causes of death differ for several of the service occupations, as shown in Table 4. Generally, the SMRs for women were higher than those for men in similar age-adjusted, race, and occupation groups. For instance, for white female and male LVNs and health aides, the respective high SMRs for all causes of death of 168 and 132 were found. Black women in these occupations also showed a high SMR, while the SMR for black men was only marginally high.

TABLE 2.—*Selected Leading Causes of Death for Women Aged 16 to 64 by Labor Force Status and Race, California, 1979-1981**

	Breast Cancer		Ischemic Heart Disease		Lung Cancer		Cancer Digestive Organs		Motor Vehicle Traffic Accidents		Cirrhosis		Suicide		Homicide	
	Rank	Percent	Rank	Percent	Rank	Percent	Rank	Percent	Rank	Percent	Rank	Percent	Rank	Percent	Rank	Percent
All Women	2	9.3	1	11.0	3	7.4	4	6.7	5	5.6	7	5.1	11	4.1	12	2.5
Non-Labor Force	2	8.4	1	12.1	3	6.3	4	6.4	9	4.6	5	5.6	11	3.7	12	2.0
Labor Force	1	10.1	2	10.1	3	8.3	4	7.0	5	6.5	8	4.6	9	4.4	12	2.9
White	1	10.6	2	10.1	3	8.8	5	6.8	4	6.9	8	4.8	9	4.7	12	2.3
Black	2	6.8	1	11.1	7	5.8	6	6.5	13	3.4	9	4.0	13	1.8	3	6.7
Asian	3	9.5	7	5.4	9	3.7	1	13.7	4	8.1	12	1.7	6	7.4	8	4.2

*From State of California, Department of Health Services, Health Data and Statistics Branch, Occupational Mortality Study File, 1979-1981.

TABLE 3.—*Standardized Mortality Ratios (SMRs) by Leading Causes of Death for Selected Occupations of Women Aged 16 to 64, by Race, California, 1979-1981*†*

	Occupations									
	White‡					Black‡				
Cause of Death by Rank	Waitress	LVNs, Aides	Cosmetologists	Housekpr, Janitor	Telephone Operator	Waitress	LVNs, Aides	Cosmetologists	Housekpr, Janitor	Launderer, Dry Clean
All Causes	247	168	168	69	171	220	135	195	138	309
1 Breast cancer	130m	124	156	31	175	...	...	...	...	...
2 Ischemic heart disease	256	201	141m	...	156	...	146	259	128	352
3 Lung cancer	368	138	188	45	191	...	...	271m	...	383
4 Cancer of digestive organs	133m	138	163	57	178	...	...	253m	129m	296
5 Motor vehicle accidents	235	188	...	...	158m	...	...	...	...	...
6 Genital cancer	191	139	182	71	...	...	...	...	...	404
7 Cerebrovascular disease	218	163	193	...	...	...	156	...	...	...
8 Cirrhosis	423	165	212	...	191	507	159m	...	165	626
9 Suicide	220	245	...	...	192	...	259	...	...	...
10 Other heart disease	314	141	192	72	...	...	...	...	148	...
11 Respiratory tract disease	430	155	...	48	234	...	...	...	148m	...
12 Other accidents	225	209	257	...	222	...	174	...	...	...
14§ Homicide	360	161	201m	...	...	...	164	...	171	...
15 Hypertensive disease	...	244	...	...	...	...	165	...	166	328
Total Number of Deaths	1,392	1,470	482	598	427	65	549	100	687	140

*From State of California, Department of Health Services, Health Data and Statistics Branch, Occupational Mortality Study File, 1979-1981.
†SMRs were standardized for age. An "m" beside a number indicates elevated but "marginal" for this study.
‡The number of Asian deaths in these occupations did not meet the minimal size of more than 50.
§There were no high SMRs for the 13th cause of death, leukemia and other lymphatic cancers.

TABLE 4.—*Standardized Mortality Ratios (SMRs) for All Causes of Death for Selected Service Occupations by Sex and Race, California, 1979-1981**†

		Women		Men	
Occupation	*Race*‡	*SMR*	*Number*	*SMR*	*Number*
LVNs and health aides	White	168	1,470	132	260
	Black	135	549	110m	119
Health technicians	White	122	264	...	152
	Black	...	34	...	31
Other health professionals	White	120	138	73	152
	Black	...	34	...	15
Housekeepers and janitors	White	69	598	87	2,253
	Black	138	687	92	937
Cosmetologists and barbers	White	168	482	110m	330
	Black	195	100	146	58
Launderers and dry cleaners	White	114m	130	...	119
	Black	309	140	177	96

LVNs=licensed vocational nurses

*From State of California, Department of Health Services, Health Data and Statistics Branch, Occupational Mortality Study File, 1979-1981.

†An "m" beside a number indicates elevated but "marginal" for this study.

‡There was one low SMR (66) for Asian male housekeepers and janitors. There were no high SMRs for Asians.

High all-cause SMRs were found for both black women and men employed as cosmetologists and barbers and as launderers and dry cleaners. In each of these occupational groups, however, the relative mortality risk for women was greater than that for men.

Age- and race-adjusted SMRs for women and men in seven industries are presented in Table 5. In each of these industries, the relative risk of death compared with the expected risk was greater for women than for men.

Discussion

Current studies indicate that women in the labor force are healthier than non-labor force women.[8,11,19,26,32] Work has a strong and positive effect on women's health, apparently separate from the "healthy worker" effect.[23,26] Recent evidence shows that, next to age, occupation is the key determinant of health for women.[17] The COMS data further show the importance of occupation in determining women's health and contribute additional evidence to support the hypothesis that women have significant variations in the risk of mortality by occupation, as well as by age and race.

According to Wingard, the variable mortality risks by

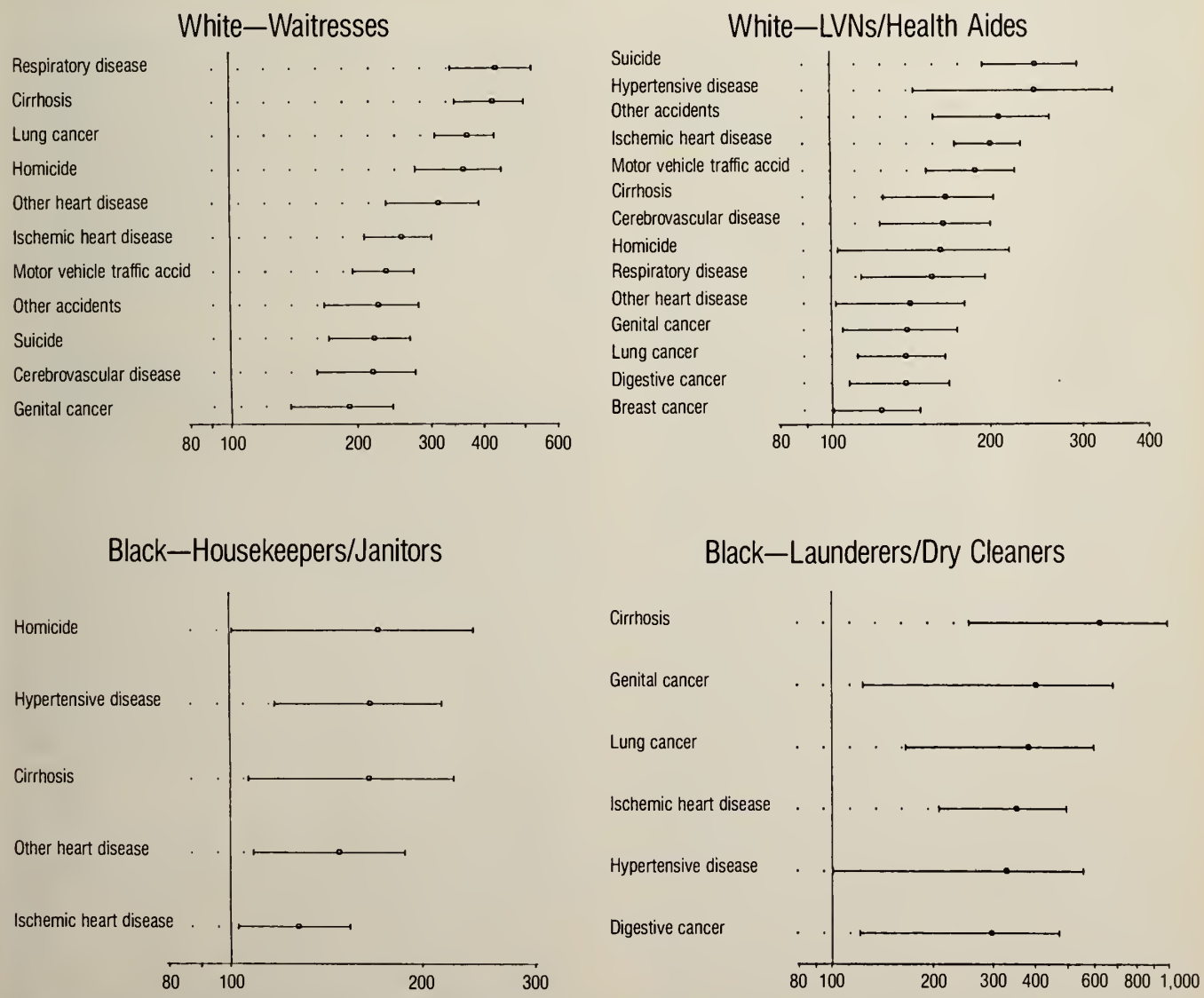

Figure 2.—The graphs show the standardized mortality ratios for women by race for the leading causes of death of selected occupations, California, 1979 to 1981. LVNs = licensed vocational nurses

TABLE 5.—*Standardized Mortality Ratios (SMRs) by Selected Industries for Women and Men, California, 1979-1981**†

Industry	Women SMR	Women Number	Men SMR	Men Number
Communications‡	123	636	71	959
Eating and drinking	173	2,285	122	3,201
Laundry and dry cleaning	163	385	105m	415
Barber and beauty shops	163	579	108m	377
Hospitals	88	2,316	71	1,248
Nursing and personal care	232	804	147	184
Other health services§	118	1,166	62	881

*From State of California, Department of Health Services, Health Data and Statistics Branch, Occupational Mortality Study File, 1979-1981.

†An "m" beside a number indicates elevated but "marginal" for this study.

‡The communications industry includes radio and television broadcasting, telephone, telegraphic, and miscellaneous communications services.

§The "Other health services" industry includes medical offices, laboratories, clinics, and miscellaneous health centers, services, and associations.

occupation depend on work exposures and on life-style, biologic, and social factors.[14] A number of authors outline similar occupational factors.[9,18,23,30,33] Most studies of women's occupational health have focused on life-style, stresses, socioeconomic factors, and women's social roles as caretaker for children and older parents.[14,34,35]

Work-related exposures that affect women's health include poorly designed and maintained equipment, extreme temperatures, job-related driving, violence at the work site, side-stream smoke, toxic chemicals, microbial agents, shift hours, occupationally associated life-style behaviors such as smoking and drinking patterns, and other work-related stresses.[9,16,17,31,34,36,37]

A number of studies have investigated women's work-related stresses, including low pay; poor benefits; shift hours; bimodal work histories; lack of professional support; lack of job control; and limited job challenge, recognition, training, and promotional opportunities.[11,12,17,22,33,38] Research findings repeatedly point to the additional workloads and stresses women face because of their dual roles as workers and mothers/housekeepers.[14,21-23,30,39] It is estimated that married women who are employed full time work 80 hours per week (including home and family responsibilities), compared with an average of 50 hours worked by their employed spouses.[31] Researchers frequently note the multitude of stresses inherent in these dual roles and the associated symptoms of nervousness and anxiety.[15,19,22,36,39,40]

Relatively few studies have looked at the relationship between the role of parenthood, work, and health for women or men.[11,14,17,21,41] Recently, increasing attention has been focused on the negative health effects for both mothers and children of inadequate maternity-related employment benefits and the lack of quality, affordable child care.[30,42]

Socioeconomic factors such as income, education, marital status, housing, diet, and the availability of adequate support services affect health and potentially confound the relationship between women's work and health status.[43-50] The societal lack of options for adequate care of children and older parents further exacerbates the pressures on women, particularly for single working women.[17,30,51] The roles, means of coping, and motivations that are culturally learned by women affect their entry into specific occupations, ability to deal with job stresses, and promotional opportunities. These structural factors in society also confound the relationship between women's work and health.[20,21,41,44,52]

These critical, work-related factors should be taken into consideration by physicians evaluating the health of working-age women. Also, our findings suggest that it is important for physicians to investigate possible occupationally based causes for women suffering from a wide variety of common diseases and injuries. A number of examples of diseases and injuries that, based on the COMS data, may be associated with occupational exposures and stresses are outlined below.

California's waitresses are at high and not previously reported risks from ischemic heart disease, suicide, respiratory tract disease, and homicide. The high SMRs found for cirrhosis, lung cancer, motor vehicle traffic accidents, and other accidents support evidence from previous studies of waitresses.[53-55] The COMS SMRs of 507 for cirrhosis among black waitresses and 423 among white waitresses warrant additional study. Employment in an occupation involving the sale of alcohol has long been associated with an increased alcohol intake.[56] Also, according to Sterling and Weinkam, about half of white waitresses were reported to smoke, and they also were likely to have been exposed to substantial side-stream smoke.[57]

The high risk of suicide for both black and white women working as licensed vocational nurses and health aides is supported by previous studies that found high risks for nurses in England and for other health workers in the United States, including physicians.[18,55,58,59] COMS data also show, apparently for the first time, a high SMR for hypertensive disease in addition to highs for other accidents, ischemic heart disease, cerebrovascular disease, and cancer of the lung, breast, and digestive organs. The Washington State study also found elevations in the number of deaths from intestinal, uterine, and kidney cancers.[53] According to Sterling and Weinkam, more than a third of white female hospital attendants smoked and, of those, more than half smoked a pack or more per day.[57]

This large occupational group of LVNs and health aides shows several high SMRs that are fairly consistent by race, yet this has not been well studied. Mortality surveillances of this group should continue. Also, additional studies should focus on potential physical exposures, as well as job-related stresses, that may contribute to these high mortality risks.

California's cosmetologists face unexpectedly high risks of death from other accidents, cirrhosis, cancer (lung, genital, breast), and heart disease similar to those found previously in the Washington State and Roswell Park (Buffalo, New York) studies.[53,60] The COMS findings suggest additional risks for this group, including cerebrovascular disease and cancer of the digestive organs. These workers routinely have exposure to a number of chemical agents, including dyes, solvents, and methacrylates.[28] Additionally, according to Sterling and Weinkam, almost half of white female cosmetologists smoked and, of these smokers, most smoked a pack or more each day.[57]

Housekeepers and janitors show different patterns of risk for blacks (high), whites (low), and Asians (not significant). The low SMRs for various cancers among white women in this group are in agreement with the findings for female housekeepers, stewards, and janitors in Washington State. Also, the high SMR for ischemic heart disease in blacks is supported by Washington data.[53] Three SMRs for blacks suggest risks that apparently have not been reported previously for this occupation: homicide, hypertensive disease,

and cirrhosis. The reasons for the differences in risk patterns by race for this group need further investigation.

Telephone operators in California show SMRs that are about twice the mortality risk expected for respiratory tract diseases, other accidents, suicide, cirrhosis, and lung cancer. These findings, along with other highs for breast cancer, ischemic heart disease, and cancer of the digestive organs, raise a question about the possible health effects from work-related exposures, including job stress. Unfortunately, little information is available with which to compare these California data.

Although no significant high or low SMRs were found for white or Asian female launderers or dry cleaners, black women in this occupational group had three to six times the expected risks of mortality from cirrhosis, genital and lung cancer, ischemic heart disease, hypertensive disease, and cancer of the digestive organs. Studies in Missouri, Wisconsin, Rhode Island, and England found elevated risks for genital and lung cancer, cirrhosis, hypertension, and ischemic heart disease among similar workers.[55,61-63] The COMS high for cancer of the digestive organs appears to be new data that should be further studied.

Conclusion

This study presents new data about mortality of women in California according to occupational groupings. Additional studies are needed to investigate a number of factors potentially related to the high mortality risks for women in certain occupations. This is especially so for confounding variables such as smoking, the use of alcohol, and socioeconomic status; toxic chemical and other hazardous substance exposures; the duration and levels of employment for women in traditional and nontraditional jobs; employment-related stress; marital status and responsibilities for children and older parents; health care access and use by employed women; and the impact of protective variables such as positive health behaviors and strong social support.

Though the mortality patterns of all causes of death in this study generally were similar for women and men by race and occupation, the specific risks shown for women were often different from those for men. Further research needs to focus on these differences to provide a more adequate information base from which more effective prevention strategies and health maintenance regimens could be designed for women. At present, women's health promotion and disease intervention programs, as well as health practices prescribed for women by physicians, often are modifications of models that were originally developed for men. To be more effective, however, such programs and practices may need to be specifically developed for women, targeting particular occupational and industry groups.

Further, to more reliably assess possible occupational health risks in California for subpopulations and of less frequently occurring diseases, death record-based occupational mortality patterns should be examined regularly. High-risk findings should be further investigated through case-control studies and targeted field investigations to determine critical occupational exposures for women.

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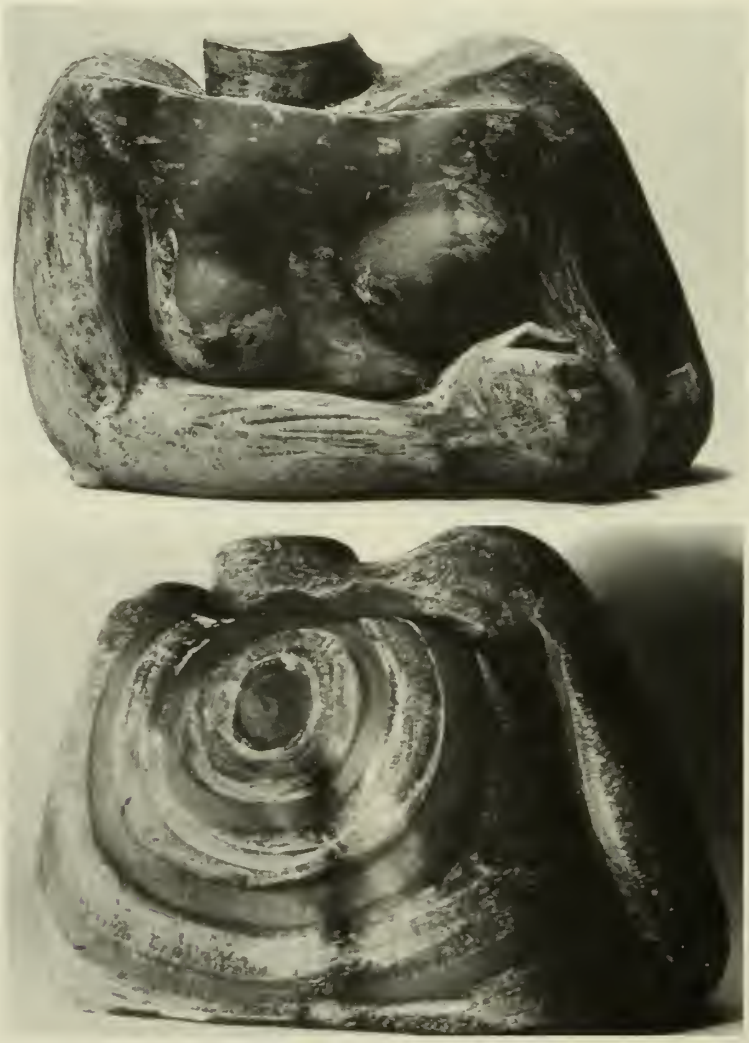

Woman Trying to Make a Point

Medium: Fired Clay

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The Risk of Multiple Addictions

Guidelines for Assessing a Woman's Alcohol and Drug Use

SHERRI MATTEO, PhD, *Stanford, California*

Psychotropic drugs have been overly prescribed for women of all ages for all manner of symptoms. Patients' and physicians' expectations about appropriate diagnosis and treatment, combined with the relative invisibility of women's alcohol and legal and illicit drug use, can lead to quick but temporary prescription solutions that may put women at risk for multiple addictions. This is a special problem for adolescent, minority, and elderly women, about whom we know little yet hold strong stereotypes. Moreover, while prescriptions may alleviate patients' symptoms, they do little to correct the underlying situation. Physicians are encouraged to review their prescribing habits and to learn more about their women patients' use of alcohol, cigarettes, previously prescribed medications, and recreational drugs, as well as a tendency to self-medicate. Physicians should also have available alternative strategies to prescribing psychotropic drugs.

(Matteo S: The risk of multiple addictions—Guidelines for assessing a woman's alcohol and drug use, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:741-745)

In recent years, increasing attention has been given to the effect of both patients' and physicians' attitudes, stereotypes, and behaviors on the delivery of health care. Researchers have identified several problem areas in which diagnosis and treatment may vary as a function of participants' sex, age, race, class, and ethnicity. One such area of differential treatment is overprescribing psychotropic drugs for women and the problems that may arise when such patients' drinking and drug use are inadequately assessed.

Women and Psychotropic Drug Use

Sex differences in obtaining and using psychotropic drugs have been well documented.[1-28] Twice as many women as men continue to receive and use prescriptions for these substances.[1,4-6,12,19,24] Women also receive more multiple and repeat prescriptions[5,20,25,29] and are more likely to be prescribed excessive dosages.[20]

Most women obtain their drugs from primary care physicians.[1,5] Prather and Fidell note other sources of drug procurement such as stealing prescription pads from physicians' offices, borrowing or stealing drugs from friends or family members, or buying street drugs.[20] Physicians may write prescriptions as a way of ending the office visit,[20] because they feel patients expect them to and will be dissatisfied if they do not,[30] as a substitute for other behavior management techniques,[30-32] or because they have a pattern of high prescribing.[11] Other studies have stressed the importance of drug advertising,[32-34] higher rates of consulting by women,[30] stereotyping of women as more prone toward emotional disorders,[5,6,28,35,36] and the salience of the reproductive role on prescribing patterns.[25]

For example, Svarstad and colleagues[25] examined pharmacy records and found that although women received more prescribed drugs than men during a two-year study period, the differences were most apparent during a woman's peak childbearing years and were directly related to reproductive functioning. Further, 71% of women, compared with 53% of men, received at least one prescription drug, with women receiving a higher number of original and refill prescriptions. While men obtain more drugs as they age, the number of different drugs and the proportion of women receiving drugs remain high across the lifespan. The authors suggest that although the higher rate of prescribing psychotropic drugs for women was not statistically significant in this study, it was not clear that women needed all the drugs they received, that their usage was solely related to the reproductive role, or that psychosocial factors did not enter into the prescribing pattern.

Most of the findings summarized thus far are from adult, nonminority women. Adolescent, minority, and elderly women have been studied far less often and yet present special considerations for diagnosis and treatment by physicians. These include age and the likelihood of concurrent drug use, cultural factors for minorities, and omitting elderly women in drug testing where results may affect patients' receiving and using psychotropic drugs.

Psychotropic Drug Use Among Adolescents

According to Kandel and Logan, a number of cross-sectional studies have shown age-related trends in patterns of legal, illegal, and medically prescribed psychoactive drugs.[37] In their study of 10th- and 11th-grade public high school

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students, boys used more drugs than girls in every category except tranquilizers and stimulants. For both sexes, prescription drug use starts out with a low rate of initiation (first time use), but this rate increases sharply and continues to rise from about age 13. At about age 20 or 21, rates for prescription drugs are higher than for nonprescription drugs, with a substantial increase in prescribed psychoactive drug use in persons in their mid-20s.[37]

Addiction does not seem to be a problem at these early ages; the rate of persistence—the length of time a person uses a drug—is less for prescription than for illicit drugs, for marijuana and cigarettes, or for alcohol.[37] Physicians should be aware, however, that young women do drink and are likely to be using other legal or illicit drugs; physicians must consider the possibility of drug interactions.

Yamaguchi and Kandel looked at factors that precede drug use.[38] In the same sample as previously described, these workers found an early use of cigarettes to be most important to women's later use of prescription drugs. For women, using alcohol or cigarettes precedes using marijuana and the three precede other illicit drug use, but it is the combination of alcohol and either cigarettes or marijuana use that best predicts a later use of psychoactive drugs.[38]

Yamaguchi and Kandel also found that the presence of depressive symptoms are important to first prescriptions for psychotropic drugs.[39] This suggests an early association is being learned between emotion management and drugs and underscores the importance of physicians' awareness of young women's substance use.

Minority Women and Psychotropic Drugs

The relatively few studies on minority women have tended to focus on Hispanics. Psychotropic drug use among Hispanic women increases with age and may be due, in part, to cultural conflicts between traditional values of remaining in the home and the emphasis in the United States on work and technology[40,41]; the pressure within Hispanic families for the woman to evidence the prestige and honor of her family through her conduct and reputation[42]; and the culturally approved practice of self-diagnosis and self-prescribing.[41,43-45]

Both physicians and patients contribute to this situation. In Hispanic culture, there is a tendency to believe in "magical thinking," with the physician playing the role of magician and pills becoming the amulets that will cure everything.[40] Some Hispanic pharmacists may contribute to the problem by selling traditional medicinal plants as well as prescription drugs without a prescription. They may even diagnose and treat patients.[40,43] These factors point to the need for physicians to use culturally sensitive questions when taking medical histories.

Elderly Women and Psychotropic Drugs

Among the elderly, little attention has been paid to the incidence and effect of psychotropic drug use.[46] The Food and Drug Administration has rarely included elderly women in studies evaluating medication, nor have drug companies included such women in their clinical trials.[15,47] Although the elderly make up only 11% of the population, they receive 25% of all prescriptions. Elderly women make a substantially greater use of prescribed psychotropic drugs and are more likely than elderly men to be given these drugs. Among the consequences are suicide, dependency and addiction, affective disturbances, insomnia, overdose, and cognitive and motor impairment.[11]

Hispanic women older than 60 years use diazepam (Valium), chlordiazepoxide hydrochloride (Librium), and chlorazepate dipotassium (Tranxene) more than other women and use them longer and with greater frequency. There is a clear relationship of age, education, and income to recency, frequency, and duration of use, with higher rates among older, unemployed, and less educated women. Black women differ in that those older than 60 reported little use of psychotropic medications of any kind. When they did use them, it was for shorter periods of time and less frequently than the other women.[46]

In summary, women have a long history of receiving and using psychotropic drugs either through prescription or other methods. This pattern can begin as early as 12 or 13 years of age and continue throughout their lives. It is possible that such patients are at risk for the development of multiple addictions or adverse consequences because of the concurrent use of other legal or illicit drugs, alcohol consumption, or all of these.

Women and Alcohol

Women's drinking patterns and problems have remained fairly invisible, especially compared with men's.[48,49] Wilsnack and co-workers found that women's drinking patterns remained relatively constant from 1971 to 1981, though there have been increases in drinking or heavy drinking in certain subgroups.[50] For instance, more women aged 35 to 64 are drinkers, and the percentage of women aged 35 to 49 who are heavy drinkers rose from 5% in 1971 to 9% in 1981. Other women have higher risks of becoming heavy drinkers or of having drinking problems develop[50-52]: young women aged 21 to 34, those women who never married, divorced or separated women, unemployed women who were looking for work, and those who lived with partners to whom they were not married. Drinking women who were housewives or who worked full-time outside the home displayed fewer alcohol dependence symptoms than women with part-time jobs.

Symptoms of depression were linked with chronic rather than heavy drinking, which in turn seemed linked to obstetric or gynecologic problems such as menstrual cycle dysfunctions, pregnancy complications, miscarriage, stillbirth, premature birth, or infertility. Still other relationships were found between drinking and social roles, with fewer roles associated with greater problems. Wilsnack and associates concluded that women's use and abuse of alcohol do not have a simple or single cause.[50]

These authors found that while current drug use does not go far in explaining their survey subjects' level of alcohol consumption, past drug use is associated with higher levels of current drinking and a greater number of adverse drinking consequences. Current heavy and problem drinking could be a substitute for previous psychotropic drug use, and those who treat these women should be aware of long-term tendencies toward self-medication, as well as current drug use.

Diagnosing Women's Alcohol Use

A number of attitudinal and behavioral factors make women's drinking patterns and problems much less visible than men's. Consequently, women are at greater risk for remaining undiagnosed or misdiagnosed and therefore untreated or for being addicted to more than one drug.

Throughout history, a double standard has existed that allows us to tolerate a drunken man but abhor a drunken woman, labeling her sexually dangerous, promiscuous, and generally out of control.[48,53] The reaction of disgust and repulsion with which an alcoholic woman must contend may well reinforce her reluctance to admit to a drinking problem. She is much more likely to drink alone, at home, early in the mornings or on weekends, to go to great lengths to hide her problem from herself and others, and to transform her problem into "nerves," seeking corroboration from physicians' prescriptions that her problem is a more legitimate one.[48] She is also more likely to be divorced or separated, making her drinking problem easier to hide.[53]

The fact that alcoholism has been viewed as an exclusively male disorder compounds the invisibility problem for female drinkers. Previous research has focused almost entirely on men by excluding female subjects from studies or averaging their data in with men's.[50,53-56] Sex differences are difficult to detect under such circumstances, and concerned researchers have called for the separation of data between men and women to assess the effects of sex and age.[51,53,57] Even current research—on children of alcoholics, for example—has underscored the connection between fathers and sons, with less attention paid to daughters of alcoholic fathers or mothers.[53]

The invisibility of women's problem drinking combined with the tendency to see alcoholism as a male domain and the reluctance of physicians to diagnose alcoholism[58] puts women at particular risk for misdiagnoses and treatment approaches that may lead to multiple addictions. For example, a woman may present with symptoms of fatigue; depression; low self-esteem; sexual problems; family, school, or job stresses; irritability; or anxiety. All are symptoms that are likely to be treated with the use of sedatives, minor tranquilizers, or other psychotropic drugs without extended questioning that might illuminate a drinking problem.[53]

Even extended questioning about alcohol consumption may not lead to a correct diagnosis. Women who are problem drinkers tend to combine alcohol with sedative dependence[53,59] and do so more frequently than men.[59] If physicians think of an alcoholic as someone who takes a morning drink, they may miss the many women for whom the morning "drink" is the morning sedative.[53]

Charts and graphs of how the body processes alcohol are usually based on data from male subjects. Thus, estimates of blood alcohol levels based on the number of drinks over time and body water content are correct for men but not for women. Physicians may misdiagnose a woman's drinking problem if they consider only the number of drinks a patient consumes. Careful and sensitive history-taking may help reduce polydrug abuse and facilitate the medical and psychological rehabilitation process.[59]

Once a drinking problem is identified, the next hurdle may be getting a woman into treatment. Unlike men, whose drinking problems are more often made visible by trouble on the job or with the law[53] and who are much more likely to come into and remain in treatment centers,[54,60,61] women typically find their way to treatment only after health problems emerge or if they are having family problems. The sources to which they turn—physicians, lawyers, and social workers—have a tremendous opportunity to help these women, however, by learning to ask the questions that will facilitate diagnosis and treatment.

Alcohol Use Among Adolescents

Several recent national surveys, reviewed by Thompson and Wilsnack,[62] indicate that most high school girls drink alcohol. In a 1983 survey, 86% of high school senior girls reported using alcohol at least once in the preceding year and 64% reported use within the previous month.[63] Of these girls, 39% reported getting moderately or very high whenever they drank. Nearly half of the girls surveyed had used alcohol on at least 10 occasions in the preceding year, 27% on 20 or more occasions, and 13% on 40 or more occasions.

Men and women increase their alcohol consumption during the college years,[64,65] although the amount decreases for women as they get older.[57,64] Younger women often drink more on more occasions, whereas older women drink less but more often.[57] Data from a follow-up to the College Drinking Study[66] showed that college women drink frequently—as opposed to heavily—to reduce tension[57] or for "feeling adjustment"—that is, to counteract shyness or recover from disappointments.[67] These women were also more likely to have drinking problems in later years.

Alcohol Use Among Minorities

Among young minority women, intermediate levels of drinking appear to be the norm. Black women were more likely to abstain, followed by Native Americans, Hispanics, and white non-Hispanics.[68] White adolescents were more likely to use and abuse alcohol than either black or Hispanic adolescents.[62]

Data on adult samples are not as representative of different minority groups and suffer from a variety of methodologic problems. Little is known, for example, about Asians or different Native American groups. From the studies that exist, Hispanic women seem to have the most difficulty with alcohol dependence but may go undiagnosed because of the cultural tendency of husbands and families to protect and shelter wives. Native American women have the highest proportion of alcohol-related deaths, including a death rate from cirrhosis that is more than six times that of white women.[68]

Alcohol Use in Elderly Women

Studies on the elderly show few drinking problems.[50] Most national studies report a higher percentage of abstainers among those older than 65 years.[69] Only 2% of women older than 65 are considered problem drinkers; given women's longer lifespan, however, and the frequency with which they are prescribed psychotropic medications, physicians are encouraged to err on the side of caution and ask about alcohol consumption.

In summary, women's drinking patterns have remained fairly consistent, with certain subpopulations showing mild increases in alcohol use. The prevalence of problem drinking among women has been difficult to assess adequately because of stigmas that reinforce hiding the problem, such as

- The tendency to see problem drinking as an exclusively male disorder;
- The preponderance of studies based on male participants;
- Research instruments geared toward male behaviors[70];
- Cultural attitudes that may shelter female problem drinkers.

Multiple Substance Abuse

Documenting the problem of multiple substance abuse has proved to be a conceptual and methodologic nightmare, but there is ample evidence for its existence. In addition to elaborating on these problems, Celentano and McQueen cite a number of findings that show the relationship between drinking and multiple drug use.[70] Of particular interest is the finding that in women, age peaks in multiple drug use coincide with peaks in heavy drinking—ages 35 to 49.[70(p107)] Further, 25% of women in treatment for alcoholism were found to have significant prescription drug problems, pointing to an increased risk for accidental overdose.

These authors lay much of the blame at the feet of funding agencies that support either drug or alcohol research but not multiple substance abuse research and social scientists who tend to specialize in one domain to the exclusion of the other. But the contributions of patients and medical personnel, however unintentional, should not be underestimated.

In addition to the questions in Dr Unger's article elsewhere in this issue, the guidelines that follow may help minimize, if not prevent, the risks of inappropriate prescribing, especially for patients who may have a high potential for chemical dependency.

Guidelines for Assessing a Patient's Alcohol and Psychotropic Drug Use

Assessment

- A section on alcohol and drug use should be included in the medical history form.
- Questions should be asked in the interview that assess a patient's general quality of life and, in particular, the patient's satisfaction with job, family, relationships, and friendships.
- The patient's perceptions of available support should be elicited, particularly if a drug or alcohol problem is suggested.
- Indirect questioning should be used to assess alcohol or drug use. Expressing concern over studies that show links between alcohol consumption and breast cancer, for example, may be a way of allowing a patient to express her concerns about her own drinking.
- Physicians should be particularly aware of adolescent drinking and drug use. Young women do drink and the amount and frequency can increase during the early college years. There is anecdotal evidence that college women frequently present at clinics feeling overly stressed and depressed and just as frequently are given ready prescriptions for psychotropic drugs without being asked about their current drug use.

Communication

- Physicians should learn to note and interpret nonverbal as well as verbal cues.
- Patients who are assigned physicians—in health maintenance organizations, for example—are less satisfied initially and may be more reluctant to talk openly.[71]
- Physicians should consider the effect advertising may have on their own prescribing patterns and on patients' willingness to use medications.

Referrals

- A list of private and community resources—treatment centers, hot-line numbers, women's centers—should be available so that a patient can seek additional information or help.
- Persons or community centers that specialize in skills training should be identified. Research has shown that interventions aimed at improving social and stress management skills effectively counter problem drinking in some groups.[57]
- Physicians should make specific and early referrals.

Education

- Physicians' reception areas should display readable pamphlets and brochures on the warning signs of alcoholism and drug abuse and on the dangers of combining certain substances.
- Discussion of these issues should be included in continuing medical education courses, conferences, medical curricula, and journal articles.

Self-Monitoring

- Physicians should watch their own prescribing patterns, possibly by keeping a log. Unless they keep close track, it is difficult to estimate prescribing patterns correctly.[72]
- They should not underestimate their ability to provide support and reassurance to a patient.
- Finally, physicians should ask themselves the hard questions. They should take the time to examine their attitudes and stereotypes toward special populations. Many have biases that are often hidden and extremely difficult to recognize.[73]

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Women and Medicine

Chemical Dependency in Women

Meeting the Challenges of Accurate Diagnosis and Effective Treatment

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Women dependent on alcohol or prescribed or nonprescribed psychoactive drugs present special diagnostic challenges to physicians. Chemical dependency likewise has adverse effects on women who are nonusers through the disease of co-dependency. The natural history of chemical dependency in women includes sex-specific differences in presenting signs and symptoms. Collateral medical history may come from a variety of community sources. Diagnoses may also use sex-specific criteria, with simultaneous diagnoses of chemical dependency and co-dependency considered.

(Unger KB: Chemical dependency in women—Meeting the challenges of accurate diagnosis and effective treatment, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:746-750)

Women impaired by chemical dependency have historically escaped public attention. Before the early 1960s and the emergence of the current women's movement, female chemical dependency was regarded as a rare manifestation of an essentially "male" disease. Thus, it was often ignored, underreported, underdiagnosed, and most certainly undertreated. Over the past 25 years, old assumptions about women have been challenged. Society has gradually come to accept two important, superficially paradoxic ideas:

- Women are different; they are not smaller-body-mass versions of men.
- Women are the same; entry on an equal basis to many formerly "male provinces" is now expected.

After studying these social phenomena of the past quarter century, scientists now indicate[1,2] that the permanent alterations in the societal roles of American women have consequences that directly affect the patterns of female alcohol and psychoactive drug use. Traditional upbringing, with the mother not employed outside the home, continues to diminish. "Housewife" mothers were long thought to "shield" youngsters from drug exposure, and an increasing number of employed mothers imply less supervised sons and daughters who then become more available as candidates for drug use. In addition, today's assertive young women are not only likely to be more frequent participants in all risk-taking behavior, including drug experimentation, but they meet diminished societal disapproval for these behaviors.

We know far less about the course of chemical dependency in women than we do in men. We know less about its antecedents, its consequences, and how it is best treated. Practically no outcome studies have been done that compare the effectiveness of different types of treatment approaches for chemically dependent women. Current knowledge is summarized here, with an emphasis on identifying and meeting those sex-specific treatment needs of women patients that can be readily incorporated by their physicians into current treatment planning.

Chemical dependency is defined as the compulsive use of one or more psychoactive substances—drugs or alcohol or both—with resulting impairment of physical health, emotional health, social functioning, occupational functioning, or intimate relationships. It is a physical disease in that it involves tolerance, withdrawal phenomena, and increasing deleterious effects on numerous organ systems. It is a mental disease because the substance(s) is ingested specifically to alter brain function and, thus, life experiences. This diminishes the capacity for self-observation and for personal growth. It is a spiritual disease in that a chemically altered person is unable to fully participate in relationships with other persons, with his or her own life in general, with our planet as a whole, and with the past, present, and future. It is a family disease because other persons who may not use psychoactive chemicals find it impossible to live in the same household with an active chemical abuser and still maintain an objective perspective. Inevitably, their sense of self-worth comes to depend on the chemically dependent person's behavior. This fourth, or family, aspect of the disease can occur in persons who use no psychoactive substances whatever. This family aspect of chemical dependency is becoming recognized as another disease in its own right—that of co-dependency.

Chemically Dependent Women

Pathophysiology

Chemical dependency is not a moral weakness. In both men and women, it is not only a disease but also an illness. Whereas a disease is a disturbance in structure or function at a molecular, cellular, or organ system level,[3] an illness consists of both a disease and a person's experience of the disease. Diseases can be explained by molecular, anatomic, or physiologic derangements alone, but an illness can occur

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either with or without demonstrable disturbances at these levels. Illnesses always have at least some of their pathology at higher cortical, intrapsychic, interpersonal, or social levels. This involvement of the higher cortex can result in an illness picture in which symptoms are out of proportion to what might be expected from objective evidence of molecular, anatomic, or physiologic derangements. It may also result in an illness that fails to respond symptomatically to appropriate treatment.

Though prevalent to some degree in all aspects of clinical care, this interweaving of physiologic derangement, intrapsychic phenomena, and societal expectations is highly characteristic of women patients who present themselves to physicians for the treatment of chemical dependency.

Both chemical dependency and co-dependency may be diagnosed in the same patient. The first three aspects—the physical, emotional or psychological, and spiritual—apply to chemically dependent persons. The co-dependent, or family aspect, may accompany this diagnosis but be hidden by more flagrant symptoms of drug or alcohol abuse. Often co-dependency is the sole diagnosis, disguised as various physical symptoms.

Co-Dependency

Co-dependency has been called a disease of relationships in which the self-esteem of one person is regulated by the distorted behavior of another. A co-dependent person is now thought to be one who has a series of characteristics that lead that person to select a life partner who is chemically dependent or otherwise dysfunctional. Co-dependent women do not believe that they are capable of being loved; they settle for being needed. They are attracted to needy partners in whom they see potential. They believe that they can fix what is wrong with them and be loved in gratitude for this. This prospect is not only a thrilling possibility but also permits the reenactment of the situation of their family of origin—but with a chance to make the ending come out differently. They believe that if they work hard enough and long enough that this time they will be loved in return. Co-dependent women are exquisitely aware of the needs of others and, being preoccupied with the needs of their partner, they are protected from an awareness of their own pain and needs.

Co-dependent family members are greater-than-average users of medical care. They are particularly likely to suffer from the stress-related medical disorders.

Psychological Features of Chemical Dependency

Chemically dependent women differ from men as a whole, from chemically dependent men, and from women who are not chemically dependent in the following ways:

- They show "learned helplessness" in that they lack hope about their lives and feel guilty and responsible for their circumstances.
- They believe that they are "worse" than chemically dependent men, and the men they know agree with this.
- They have a more traditional and rigid view of appropriate female behavior and are acutely aware of their failure to live up to it.
- They find the transition into treatment so enormously disruptive that it is often the cause of treatment dropout.
- They have less education, make less money, are less likely to have health insurance, and have fewer life options. Thus, they are more likely to stay in dangerous, demeaning, and drug- or alcohol-abusing situations.
- They are more likely to have come from disturbed families marked by drug or alcohol dependency, mental illness, suicide, family violence, and personal physical or sexual abuse.
- They are less involved in criminal activity and are less likely to have drunk-driving arrests. They are, therefore, less often assigned to treatment diversion programs as a result of criminal activity.
- They are much more likely to have a husband or other life partner who is a drug or alcohol abuser or both.[4]

Clinical Course

What little we know about the sex-specific aspects of drug dependency and metabolism comes largely from studies on alcoholism. Women apparently begin misusing alcohol at a significantly later age than men but become dependent at the same life stage, while drinking less.[5] Dietary factors, with high saturated fats and low polyunsaturated ones providing some "protection" from cirrhosis,[6] are documented in men, but the possibly protective effect of female hormones is not. In some early literature, women appeared to achieve a higher blood alcohol concentration per unit of ingestion than did men, but this did not hold true when corrected for the sexes' differing total body water content. An apparent "telescoping," or more rapid downhill course of alcoholism, is clearly evident: women start drinking alcohol at a later age, catch up fast, and get just as sick as the men do at about the same time of life or earlier.

Current literature suggests that alcohol dependency disrupts the lives of women more profoundly than it does those of men, suggesting that other drugs of abuse tend to do the same.

Women need not even be particularly aggressive in seeking an addiction career, for it may seek out them. According to O'Donnell and colleagues,[7] drug dependency is more likely to be established in the husband and then transferred to the wife, rather than vice versa. Addicted women are far more likely than addicted men to be married to, or romantically attached to, other addicts.[8] Although addicting chemicals have long been seen as sexualized—most street drugs have undeserved reputations as aphrodisiacs—changing fashions periodically demonstrate a unique form, and a new wrinkle in the courtship process has been documented[9]: Surveyed callers to an 800-COCAINE hotline indicated that cocaine has become accepted as a courtship ritual gift, just as were the more traditional candy and flowers. Of surveyed women callers, 87% had been introduced to cocaine use by men.

Primary Prevention

Kandel and Yamaguchi,[10] observing the initiation of both prescribed and illicit drug use in adolescents and its longitudinal history, followed a population of 15-year-old New York State high school study subjects for ten years. Their findings indicated that almost 20% of the students of both sexes had used alcohol by age 10 and more than 50% by age 14. A similar initiation-of-use rate was shown for cigarettes. Marijuana use was initiated at about age 13. Rates for initiating the use of all three of these drugs climbed until age 18, when a sharp dropoff occurred, followed by a pattern of stabiliza-

tion of the amount of use in those who continued to use the substance(s).

Important for all physicians is the finding that the initiation of prescribed psychoactives use occurred largely in the female population, beginning at a later age—around 18.[10] This is the very same period at which the initiation of illicit drug use started to decline. The rate of prescribed psychoactive drug use continued to rise in women after age 18. Psychoactive drugs were in current use by 13% of women studied at age 23.

In turn, this prescribed drug use was found to occur most readily in women who already had a past or present use of illicit drugs in their personal history. These young women not only showed depressive symptoms but gave familial histories of a maternal use of psychoactive drugs.[10] The researchers concluded that the prescribing of "minor" tranquilizers by physicians appeared to be an important factor in the course of addiction in women and thus a potential locus for preventing drug abuse.

Diagnosing Chemical Dependency

Chief Complaints

Chemically dependent women differ from other women patients in the following ways:

- They are not likely to recognize that drug or alcohol use is a source of problems in itself. They see such use as a way of coping with losses, with family problems, with a bad or violent relationship with a partner, and with medical illness, child-related stresses, or poverty.
- They fail to see how drug or alcohol use makes problems substantially worse.
- They see their drug or alcohol use as part of a solution, or as an attempt to cope with whatever is the "real" problem.
- They are more likely to seek help for problems other than drug or alcohol use. They do this first through social service agencies, not physicians. Seeking some form of help for children is a common presentation.
- They are more likely than men to have difficulties with drugs that are more socially acceptable—alcohol, for example. For this reason, their difficulties are often initially not seen as problematic because their drug is one used moderately and appropriately by most persons.
- The social stigma attached to admitting drug or alcohol problems encourages them to mislabel their problems.[11]

Medical History Taking

A physician can easily improve the taking of an adequate history in this area by incorporating one or more of the MAST, CAGE, or FOY tests in the initial evaluation of every nonpediatric patient (Figures 1, 2, and 3).[12-14] These simple, self-administered tests can be included in the medical history forms filled out by a patient.

Chemically dependent women experience more medical complications of chemical dependency than men do. They are more likely to present to their physicians with physical complaints. Most common are constitutional symptoms: headache, dizziness, abdominal or extremity pain, and requests for checkups on vague indications. Along with their physicians, they are unlikely to recognize the role that chemical dependency plays in their presenting symptoms and, like most women, they believe in the efficacy of medical treatment—more so than do men.[11]

Differential Diagnosis

A clue for physicians considering the differential diagnosis of chemical dependency is found in a clinical course in which symptoms do not improve, in spite of adequate diagnostic workup, prescribed treatment, and patient education. This may occur in a patient diagnosed as having either chemical dependency or co-dependency. At such times, a simultaneous diagnosis of co-dependency must be reconsidered. By the persistence of her dysphoric symptoms, a patient may be indicating that a second diagnosis has been missed.

Improving the Rate of Diagnosis

A "diagnosis" of chemical dependency is often first made by members of a woman's community, often long before she reaches the attention of any medical care giver.[11] They may include divorce attorneys, social workers from child protective services, the staff of battered women's shelters, or hospital emergency department personnel. Other knowledgeable people may be their children's teachers (through parents' nights, the Parent-Teachers' Association, or required school volunteer service by parents), the staff of preschools, day-care center staff, and others in the community, such as neighborhood beauticians, neighborhood pharmacists, aerobics instructors, weight-reduction salon staff, community college and continuing education teachers (especially for child development, psychology, and law-for-the-layperson classes), and local Al Anon, Nar Anon, and Overeaters Anonymous groups. These people are stunningly accurate in their diagnoses, but do not know what to do with their information. Physicians are wise to give serious consideration to any incidental, perhaps unexpected, contributions to the comprehensive medical history of a patient provided by such sources.

Physicians can also improve their rates of diagnosis if they raise their level of suspicion for patients giving medical histories that place them in one of the high-risk groups for substance abuse: incest survivors, members of genetically vulnerable families, women with chronic pain, spouses of practicing alcoholics, and battered women.[11] Physicians must be aware of the common intercurrent physical disorders by which many women express their underlying chemical dependency: eating disorders and agoraphobia. The accuracy of diagnoses may also be improved by physicians letting

CAGE Test

- Have you ever felt you should *C*ut down on your drinking?
- Have people ever *A*nnoyed you by criticizing your drinking?
- Have you ever felt bad or *G*uilty about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (*E*ye opener)?

Figure 1.—The CAGE test: A "Yes" answer to 2 or more of the questions indicates a problem with alcohol use (from the American Psychiatric Association[13]).

FOY Test

- Do your *F*riends ever worry about your drinking?
- Do *O*thers ever worry about your drinking?
- Do *Y*ou ever worry about your drinking?

Figure 2.—The FOY test (from Talbott[14]).

their patients know that they are both knowledgeable and interested in problems of chemical dependency. This simple maneuver serves to encourage patients to inform their physicians about these health issues in their lives—and at an earlier stage of the disorder. This can be accomplished by the presence of outreach educational brochures in physicians' waiting rooms.

Selected periodicals in a physician's waiting rooms can signal the physician's interest in chemical dependency health problems. These can include the Alcoholics Anonymous magazine, *Grapevine,* and the publication, *Changes,* which is directed at adult children of dysfunctional families. A discreet sign stating a willingness to discuss chemical dependency problems may be in order.

Treatment of Chemically Dependent Women

As with all patients, medical treatment begins with establishing a good physician-patient relationship.[15] It is necessary to respect a patient's own beliefs about the physical or external causes of her distress and her chemically dependent behavior. Given her low self-esteem, too-early confrontation of her denial of drug or alcohol misuse may lead to more entrenched convictions and her dropping out of treatment. It is better for the physician to praise her for having done something about her problems—that is, by seeking help—without disputing the validity of her complaints. Once an atmosphere of trust is established, it is easier to convince a patient that her alcohol or drug use is not helping but is making things worse. She may then be motivated to accept treatment for this aspect of her problems that is readily under her control. In the light of a revealed alcohol or drug misuse pattern, assisting patients to relabel their presenting symptoms is appropriate.[16] Although most people experience minor pains or sensory disturbances in the course of each day, to chemically dependent patients, all such symptoms are "labeled" abnormal and something with which they cannot cope without their self-prescribed dose of psychoactive substance. Assisting them to relabel these discomforts as normal will render them bearable.

Not all physicians have the time and the medical practice setting requisite for confirming their diagnostic suspicions, nor for personally treating all of the chemically dependent patients they see. Such physicians serve their patients well by a prompt and timely referral to a definitive treatment resource. By doing so, they may well earn the profound gratitude of both patients and their families.

Information Resources for Practicing Physicians

• California Medical Association's Chemical Dependency Education Program for Physicians

This is a continuing medical education program on alcoholism and other drug dependencies, designed for hospital medical staffs. The program consists of four one-hour modules that address physicians' attitudes on chemical dependency, early diagnosis, confirming the diagnosis and initiating treatment, and physicians' role in recovery. This program is authorized for up to four hours of continuing medical education, category I, credit. For more information or to make arrangements for presentation of the program, contact Ms Fern Leger, California Medical Association, PO Box 7690, San Francisco, CA 94120-7690; (415) 541-0900, extension 417.

• "Health Tips on Substance Abuse"

Published by the California Medical Education and Research Foundation, these are prepared by physician members of the California Medical Association and are free to its

MAST Test

Do you feel you are an abnormal drinker?	Yes ☐	No ☐	(2)
Have you ever awakened the morning after some drinking the night before and found that you could not remember a part of the evening before?	Yes ☐	No ☐	(2)
Does your spouse (or parents) ever worry or complain about your drinking?	Yes ☐	No ☐	(1)
If you stop drinking after one or two drinks, is there a struggle? Do you really want more?	Yes ☐	No ☐	(2)
Do you ever feel bad about your drinking?	Yes ☐	No ☐	(1)
Do friends or relatives think you are an abnormal drinker?	Yes ☐	No ☐	(2)
Do you ever try to limit your drinking to certain times of the day or to certain places?	Yes ☐	No ☐	(0)
Are you unable to stop drinking when you want to?	Yes ☐	No ☐	(2)
Have you ever attended a meeting of Alcoholics Anonymous (AA)?	Yes ☐	No ☐	(5)
Have you gotten into fights when drinking?	Yes ☐	No ☐	(1)
Has drinking ever created problems with you and your spouse?	Yes ☐	No ☐	(2)
Has your spouse (or other family member) ever gone to anyone for help about your drinking?	Yes ☐	No ☐	(2)
Have you ever lost friends or girlfriends/boyfriends because of drinking?	Yes ☐	No ☐	(2)
Have you ever gotten into trouble at work because of drinking?	Yes ☐	No ☐	(2)
Have you ever lost a job because of drinking?	Yes ☐	No ☐	(2)
Have you ever neglected your obligations, your family or your work for 2 or more days in a row because you were drinking?	Yes ☐	No ☐	(2)
Do you ever drink before noon?	Yes ☐	No ☐	(1)
Have you ever been told you have liver trouble? cirrhosis?	Yes ☐	No ☐	(2)
Have you ever had delirium tremens ("DTs"), severe shaking, heard voices, or seen things that weren't there after heavy drinking?	Yes ☐	No ☐	(2)
Have you ever gone to anyone for help about your drinking?	Yes ☐	No ☐	(5)
Have you ever been in a hospital because of drinking?	Yes ☐	No ☐	(5)
Have you ever been a patient in a psychiatric hospital or on a psychiatric ward of a general hospital where drinking was part of the problem?	Yes ☐	No ☐	(2)
Have you ever been seen at a psychiatric or mental health clinic or gone to a doctor, social worker, or member of the clergy for help with an emotional problem in which drinking had played a part?	Yes ☐	No ☐	(2)
Have you ever been arrested, even for a few hours, because of drunken behavior?	Yes ☐	No ☐	(2)
Have you ever been arrested for drunk driving or driving after drinking?	Yes ☐	No ☐	(2)

Figure 3.—The MAST test: Points are scored as indicated for all Yes answers. Any score above 4 is considered pathological drinking (from Talbott[14]).

members. Written in layperson's language, these sheets are formatted for easy reproduction and distribution in physicians' offices.

- National Clearinghouse for Alcohol and Drug Abuse Information, PO Box 2345, Rockville, MD 20852

A mailing list for the "Announcement of New Publications." Free, single copies of these will be sent on request. Publications include basic science, practical patient care techniques, patient education, and the like.

- 1987-1988 National Directory of Alcohol, Drug Abuse and Other Addictions Treatment Programs

Published by the US Journal of Drug and Alcohol Dependence, *3201 SW 15th Street, Deerfield Beach, FL 33442. They also publish a patient education magazine,* Changes.

- Drug Abuse and Alcoholism Newsletter

Published by the Vista Hill Foundation, 3420 Camino del Rio North, Suite 100, San Diego, CA 92108. A free four-page monthly publication, each issue focuses in detail on one aspect of chemical dependency. Topics range from the subcellular to major societal trends.

- About AA

Published by Alcoholics Anonymous, Box 459 Grand Central Station, New York, NY 10163. A free, one-page quarterly newsletter for medical professionals, it describes the various AA services and their attempts to meet the needs of special groups. They also publish Grapevine, *a monthly magazine for recovering alcoholics.*

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Women and Medicine

A Woman's Heart

An Update of Coronary Artery Disease Risk in Women

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Coronary artery disease accounts for a third of all deaths in women. Traditionally, studies on this disease have been conducted with male subjects. A growing body of evidence indicates that oral contraceptive and postmenopausal estrogen use present risk factors for the disease that are unique to women. In addition, sex differences exist with regard to the relationship of most of these risk factors to the development of the disease. An understanding of these differences has an important role in expanding the management of coronary artery disease risk reduction for women and in defining directions for future research.

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Coronary artery disease is well recognized as the leading cause of death in men. Although women have been considered to be protected from the disease, they are not immune from it.[1] Each year nearly 250,000 women in the United States die of events related to coronary artery disease, including cerebrovascular accidents.[2] This accounts for a third of all female deaths.

Despite the rise in the death rate from heart disease as a woman ages, 200,000 such deaths occur prematurely (before the age of 65 years).[3] This statistic emphasizes the importance of the disease in women as a major issue in preventive cardiology. The goal of preventive care is to postpone the occurrence of chronic disease events. Therefore, it appears that a considerable amount of mortality and morbidity could be reduced in the female population by preventive intervention involving modifiable risk factors.

Whether preventive cardiology measures can reduce the incidence of coronary artery disease in women is not clearly established for all recognized risk factors. Most of the scientific research involving prevention of the disease has been done in male subjects. Because men represent the high-risk sex with respect to coronary artery disease, in consideration of cost- and time-effectiveness, the study of the disease has generally been restricted to men.

Uncertainty exists whether research regarding coronary artery disease can be extrapolated from men to women. Most of the recommendations for risk intervention in women, however, have been based on studies involving male subjects. Despite these uncertainties, population trends of coronary artery disease events in women suggest that its risk can be modified in the female population. Since 1963, women in this country have experienced a 43% drop in deaths from both myocardial infarction and cerebrovascular accident.[3] Most of this decline has occurred since 1972. These trends in the incidence of heart disease may reflect the contemporary reductions in saturated fat intake and cigarette smoking that occurred in our population during this period.[4]

In general, the relationship of coronary artery disease events to risk factors in women appears to be similar to that in their male counterparts with respect to major modifiable risk factors such as high plasma cholesterol levels, cigarette smoking, and hypertension. The role, however, of other coronary artery disease risk factors such as diabetes mellitus, the use of estrogen hormones, physical activity, personality and stress, obesity, and even pregnancy in promoting the disease may be different and unique for women. The purpose of this article is to review the current knowledge of the risk of coronary artery disease as it relates to women. The current explanations for the male-female difference in that risk will be considered, as will the role of the individual risk factors in women. An understanding of these differences has an important role in expanding the management of risk reduction for women and defining directions of future research.

Female Protection

The process of atherosclerosis begins in childhood. The period of life when sex differences in coronary artery disease risk occur is uncertain. The difference in the incidence of myocardial infarction between adult men and women corresponds to differences noted in the extent of atherosclerosis at autopsy. A comparison of the percent of aortic surface involvement by atherosclerotic lesions from autopsy findings indicates that men have approximately 50% more atherosclerosis than women.[5]

The sex difference in the disease incidence has been attributed to "female protection." Included under this nebulous umbrella are both male-female psychosocial and biologic differences.[6] Biologic factors, in particular gynecoid hormones, appear to have a major role in promoting female protection.[7] Plasma lipid and lipoprotein levels bear impor-

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
LDL = low-density lipoprotein
MRFIT = Multiple Risk Factor Intervention Trial
NCEP = National Cholesterol Education Program
VLDL = very-low-density lipoprotein

tant relationships to coronary artery disease risk that will be considered in more detail later. Female protection appears to be mediated by hormonally induced changes in plasma lipids and lipoproteins. Specifically, estrogen appears to confer female protection through its role in promoting increases in the cardioprotective high-density lipoprotein (HDL) cholesterol. Two lines of evidence support this explanation. Population studies indicate that sexual maturation is associated with a sex-related divergence in plasma lipoprotein profiles.[8,9] At puberty, levels of low-density lipoprotein (LDL) cholesterol and HDL cholesterol decrease in both boys and girls, but the decrease in HDL cholesterol is much greater in the boys.

Second, estrogen administration has been shown to promote increases in HDL cholesterol.[10-13] The interpretation of the pharmacologic effects of estrogens on plasma lipids and lipoproteins may be different from physiologic effects. While the precise mechanism of female protection needs to be more clearly defined, it appears that the biologic effects of estrogen on plasma lipids and lipoproteins represent an important aspect of female protection. In addition, there may be male-female psychosocial differences that affect the atherosclerotic process and susceptibility for coronary artery disease.

Plasma Lipids and Lipoproteins

Elevated plasma cholesterol levels are a well-established risk factor for coronary artery disease. Studies in male subjects with hypercholesterolemia—a cholesterol level greater than 6.76 mmol per liter (260 mg per dl)—indicate that reductions in the plasma cholesterol level reduce coronary artery disease events.[14,15] Whether reducing plasma cholesterol levels in women lowers heart disease risk has not been directly shown. The Framingham study, however, has shown that elevated plasma cholesterol values are related to an increased incidence of coronary artery disease events in women younger than 50 years.[16] In this population, while plasma HDL-cholesterol levels were higher in the women than in the men, HDL cholesterol remained the strongest lipid predictor of coronary artery disease in both sexes.[17] The ratio of the total cholesterol level to the HDL cholesterol has been developed to enhance the heart disease predictive capability of these two measurements. Increasing total cholesterol to HDL-cholesterol ratios are predictive of an increasing rate of such events in women aged 60 to 69 years.[17]

Hypertriglyceridemia as a risk factor for coronary artery disease has long been a controversial issue.[18] Multivariate analysis techniques in male subjects have been unable to show a significant relationship between plasma triglyceride levels and disease events. This has been attributed to triglyceride interaction with more powerful risk factors. In particular, the low levels of plasma HDL cholesterol that generally occur concomitantly with hypertriglyceridemia may reduce the strength of the relationship of plasma triglyceride values to disease risk by multivariate analysis. Data from the Framingham study, however, indicate that for women, but not for men, hypertriglyceridemia appears to be an independent coronary artery disease risk factor on multivariate analysis.[17,19]

While women enjoy more favorable lipoprotein profiles than men, a beneficial reduction in plasma cholesterol levels is indicated for women with high-risk levels. The National Cholesterol Education Program (NCEP) recently established definite high-risk values for total plasma cholesterol as 6.24 mmol per liter (240 mg per dl) and a desirable plasma cholesterol level below 5.20 mmol per liter (200 mg per dl).[20] Therapeutic intervention strategies for the management of lipid disorders (beyond the scope of this article) are presented in the NCEP panel's report.[20] While these recommendations are based primarily on studies of male subjects and may appear to be directed towards men, they were meant to be applied to both women and men.

Cigarette Smoking

The relationship of cigarette smoking to coronary artery disease risk is well established.[21,22] The Nurses' Health Study showed a greater than fivefold increase in fatal myocardial infarction events in women smokers compared with nonsmokers who were followed prospectively over a six-year period.[23] Conversely, the cessation of cigarette smoking by women smokers returns their risk of myocardial infarction to that of women who never smoked.[24] Despite the decrease in cigarette smoking since the Surgeon General's antismoking statement in 1964, this reduction has favored men.

Although women smokers tend to smoke fewer cigarettes than men smokers, recent smoking trends indicate that since 1980 younger women—aged 20 to 24 years—appear to be increasing their cigarette consumption, both in terms of the total number of women smoking and the number of cigarettes smoked per person.[25] This finding is especially disconcerting because women in this age bracket tend also to be users of oral contraceptives. After accounting for age, the risk for myocardial infarction in oral contraceptive users who smoke more than 25 cigarettes a day is almost eightfold above that in nonsmoking oral contraceptive users and 40 times greater than the risk for nonsmoking women not using oral contraceptives.[26] This risk is even higher with increasing age. Clearly more effort is needed to prevent smoking in young women, who are currently being targeted by the tobacco industry.

Blood Pressure

The trends in blood pressure management over the past decades reflect the medical care system's recognition of elevated blood pressure as a risk factor for coronary artery disease. Since the early 1960s, mean systolic blood pressures have dropped from 129 to 123 mm of mercury among white and 138 to 123 mm of mercury among black women of ages 25 to 74 years.[27] In addition, there has been a significant decline in the prevalence of definite high blood pressure—systolic pressure, 160 mm of mercury or higher; diastolic pressure, 95 mm of mercury or higher—for both groups since the early 1970s after adjusting for aging. This has been related to increased therapeutic intervention in blood pressure management, as there has been an increase in the percentage of women diagnosed with hypertension, receiving antihypertensive medications, and whose hypertension was controlled with medication during this time period.

Evidence from the Framingham study has indicated an increase in successful hypertensive treatment since 1960.[28]

Associated with successful treatment was a significant decline in coronary artery disease events in treated women compared with untreated hypertensive women. This difference was particularly pronounced for women whose previous systolic blood pressures were above 180 mm of mercury.

Although the importance of the relationship of isolated systolic pressures to coronary artery disease risk has been controversial, the Framingham data indicate that the prevalence of isolated systolic hypertension, which increases in both sexes after the age of 55 years, is greater in women.[29] In this study, an elevated isolated systolic blood pressure was predictive of coronary artery disease for women older than 55 years.

An interesting facet of sex differences in the relationship of hypertension to heart disease risk is that the prognosis of essential hypertension (when comparisons are made between groups with equivalent age and severity of disease) is better for women than for men.[30] This finding has been attributed to the presence of more severe atherosclerotic disease concomitant with hypertension in the men, which could aggravate the effects of hypertension on the disease.

More recently there are data that indicate that the hemodynamic events which occur in persons with hypertension when subjected to isometric exercise stress testing are different for men and women.[31] Isometric handgrip exercise in 100 women with hypertension matched to 100 men by mean arterial pressure, age, race, and body surface area induced a significantly greater mean arterial pressure and total peripheral vascular resistance in the men compared with the women subjects. These findings are consistent with other reports that estrogen therapy in women can reduce blood pressure[32] and that women with higher blood estrogen levels experienced less increase in arterial blood pressure when experimentally subjected to increasing mental stress.[33] These findings may be particularly relevant in explaining sex differences that are noted with respect to coronary artery disease and psychosocial stress. Perhaps reactivity in hemodynamic responses to physical and emotional stress is more critical to disease prognosis than is the resting blood pressure value.

A particular issue of blood pressure and women involves the use of oral contraceptives containing progestinal agents in addition to estrogen. Cross-sectional data indicate that oral contraceptive use is associated with a 2.7 times higher incidence of hypertension compared with that in women not using oral contraceptives. A 5- to 6-mm-of-mercury greater systolic pressure and 1- to 2-mm-of-mercury greater diastolic pressure persisted in the oral contraceptive users who continued to use the pills on follow-up examinations.[34] An increase of more than 10 mm of mercury in the systolic pressure and of almost 10 mm of mercury in the diastolic pressure has been reported with the use of oral contraceptives over a three-year period.[35] The blood pressure generally returned to pretreatment levels within three months of stopping the use of oral contraceptive medication.

The importance of treating hypertension is well established. Current therapeutic regimens are being reassessed, however, in view of reported unfavorable effects of certain antihypertensive medications on plasma lipids and lipoproteins.[36] Although this issue is currently under critical appraisal, it would seem prudent not to defer medical management of a patient with definite hypertension because of these concerns. Selecting antihypertensive medications with the least lipid-altering effects is a sensible approach.

Diabetes Mellitus

The presence of diabetes mellitus is an important risk factor for women older than 45 years.[21,37] Persons with diabetes appear to have a twofold increase in coronary artery disease risk compared with those without diabetes, adjusting for age, systolic blood pressure, cigarette smoking, total cholesterol levels, and left ventricular hypertrophy.[38] Because the incidence of diabetes mellitus is greater among women than among men, this risk factor is of considerable importance for women.[2,38,39] In addition, the death rate from myocardial infarction for diabetic women exceeds that for diabetic men.[37] Another concern for the female population is the increase in reported incidence of diabetes mellitus in women since the early 1960s.[40] These findings emphasize the importance of the early recognition of diabetes mellitus, particularly for women.

Overweight

Defining obesity as being equal to or greater than the 85th percentile of the body mass index—weight in kilograms divided by height in meters squared—of 20- to 29-year-old men and women, 24% of women (compared with 14% of men) between the ages of 18 and 74 years are obese.[41] The role of obesity and overweight has long been recognized for its deleterious influence on other coronary artery disease risk factors such as diabetes mellitus and low plasma HDL-cholesterol levels, which represent confounding variables in interpreting obesity and heart disease risk.[42,43] The relative weight expressed as a percentage of desirable weight was shown to be an independent risk factor in a cohort of 2,818 women over a 26-year period.[44] The percent body fat has been shown to increase with age from 20% in 18-year-old women to 30% to 40% during adult life. Likewise, the incidence of obesity increases by almost threefold during this period until leveling off around the age of 65 years.[45] Trends in the incidence of obesity in women are somewhat encouraging. While 25.1% of women aged 20 to 74 years were defined as obese in 1960, the incidence had dropped to 23.8% by 1974.[41] The socioeconomic status appears to have a substantial impact on obesity, as excess body weight is reported to be up to 12 times more frequent in women of lower socioeconomic than of high socioeconomic classes.[46] A continued emphasis on reducing body fat in overweight women is needed in addition to the development of appropriate weight standards and tools that conveniently measure body fat.

An interesting note is differences between female (gynecoid) and male (android) fat distributions expressed by the ratio of the waist to hip circumference with respect to the coronary artery disease risk in women.[47] The waist/hip ratio measured in 1,462 women was more strongly associated with coronary artery disease events over a 12-year period than were indices of obesity (body mass index and sum of skin-fold measurements). The relationship of the waist/hip ratio to disease events persisted with multivariate analysis of traditional coronary artery disease risk factors.[47] The android (high waist/hip circumference ratio) distribution is associated with higher incidences of coronary artery disease than the gynecoid (low waist/hip circumference ratio) distri-

bution in both men and women.[48,49] These findings may be useful to clinicians for identifying heart disease risk.

Exogenous Hormones

Although biologic levels of female hormones appear to exert a protective effect, the role of exogenous hormones on coronary artery disease risk is being defined. These exogenous hormones include both oral contraceptives and postmenopausal estrogen replacement. The declining prevalence in the use of oral contraceptives in women of all age groups between 1970 and 1980 mainly reflects a decreased use among married women because increased use is reported among single and never-married women.[50,51]

The effects of oral contraceptives on plasma lipid levels represent the combined effects of the hormonal constituents, estrogen and progestins. Early reports indicated that oral contraceptives containing high doses of estrogen caused an increased incidence of myocardial infarction,[52-55] which is particularly increased by concurrent cigarette smoking.[26,52,54,55] Because of the often disparate biologic effects of estrogen and progesterone, it is important to consider the relationship of oral contraceptive use to coronary artery disease risk factors in terms of the individual estrogen and progestin components. Estrogen appears to raise plasma triglyceride and HDL-cholesterol levels, and progestinal agents lower the HDL cholesterol.[11-13] An additional risk potentiation from oral contraceptive use, which may contribute to atherogenesis, is an increased ratio of very-low-density lipoprotein (VLDL) cholesterol to VLDL triglyceride that occurs with the use of progestin-predominant pills.[12] The newer low-dose oral contraceptives (lower estrogen) appear to have a neutral effect on HDL-cholesterol levels.[13] Oral contraceptive use can also increase plasma triglycerides and blood pressure[35,56] and aggravate diabetes mellitus.

Estrogens are commonly taken after the menopause to reduce menopause-related symptoms. The relationship of this practice to the risk of coronary artery disease is unclear. The postmenopausal use of conjugated and esterified estrogens is associated with increased levels of plasma HDL cholesterol.[11] Because biologic levels of estrogen are associated with premenopausal risk reduction, it would seem that estrogen replacement for postmenopausal women would have a role in reducing risk. This notion is supported by findings that among women with surgically induced menopause (bilateral oophorectomy), a greater relative risk of a subsequent myocardial infarction was noted for the women who had had an operation at younger ages.[57] In a similar line of evidence, a comparison of the incidence of coronary artery disease in a group of women younger than 35 years at the time of either bilateral or unilateral ovariectomy revealed a disease incidence of 25% in the bilateral ovariectomy group versus a 3% incidence in the unilateral ovariectomy group over the ensuing 20 years.[58]

Data from case-control studies on the relationship of the risk of myocardial infarction in women using postmenopausal estrogen are conflicting.[59-62] Evidence from the Lipid Research Clinics study supports a coronary artery disease risk reduction associated with postmenopausal estrogen use.[63] This study noted a third lower relative incidence of myocardial infarction deaths with estrogen use compared with nonuse in women aged 40 to 69 years over an 8.5-year period after adjusting for potential confounding factors.[63] This contrasts with an earlier report from the Framingham study that indicated a doubled incidence of myocardial infarction and of cerebrovascular accident among estrogen users compared with nonusing counterparts.[64] When the Framingham study data were adjusted for smoking, however, the risk for myocardial infarction disappeared but the risk for cerebrovascular accident persisted.[65] An important aspect in interpreting these disparate findings involves issues of the type and dose of estrogen used and the duration of estrogen therapy.

On the other hand, estrogen supplementation in men does not decrease the incidence of coronary artery disease compared with placebo and may actually increase the incidence of adverse medical effects.[66] More study is indicated to clarify the role of postmenopausal estrogen use in women because the effects of estrogen replacement may be related to the type of estrogen given and also to the timing of replacement with respect to the start of menopause.

Physical Activity

Physical inactivity is recognized as a coronary artery disease risk factor in men.[67] The Harvard alumni study has established that men who expend greater than 2,000 calories a week through leisure-time physical activity have a reduced incidence of heart disease events when compared with sedentary—less than 500 calories a week—counterparts.[68] These findings are confirmed by a recent publication of the Multiple Risk Factor Intervention Trial (MRFIT).[69] Whether these findings apply to women has not been clearly established.

Current exercise training recommendations formulated by the American College of Sports Medicine are based on exercise regimens designed to increase maximal aerobic work capacity ("The Recommended Quantity and Quality of Exercise for Developing and Maintaining Fitness in Healthy Adults," American College of Sports Medicine position statement, 1987). With respect to coronary artery disease risk factor modifications, exercise training studies in men indicate that aerobic exercise training has favorable effects on plasma lipoproteins by raising the HDL-cholesterol level.[70] Regular exercise also may reduce the blood pressure and control body weight. In contrast to studies in men, exercise training studies in women have not uniformly shown an increase in HDL-cholesterol levels in women either before or after the menopause.[71-74] The reason for this difference in sex responses to exercise training with respect to HDL-cholesterol levels is unclear but has been attributed to intrinsically higher HDL-cholesterol levels in women. Greater exercise training-induced increases in HDL cholesterol are shown in women with low preexercise training HDL-cholesterol levels than in women with higher pretrained values.

A current issue in the areas of exercise and health promotion is findings that suggest that the sort of physical activity needed to lower heart disease risk may be of lower work intensity than what is currently recommended. The MRFIT study indicated that despite a reduction in coronary artery disease events in men who were more physically active based on leisure-time activities, less than 5% of the total group achieved the intensity of physical work currently recommended for exercise training.[69]

Although comparable studies with respect to leisure-time physical activity and heart disease have not been done in women, the relationship of physical activity to coronary risk factors in postmenopausal women indicates that physical ac-

tivity as measured by the Paffenbarger index is significantly related to increasing HDL_3 cholesterol but not HDL cholesterol or HDL_2 cholesterol.[75] On the other hand, when the sports activity index component of a questionnaire was used, a significant positive correlation was found between increasing sports activity and HDL cholesterol and the HDL_2-cholesterol but not the HDL_3-cholesterol subfraction. This indication that higher work intensity levels may be necessary in women to effect increases in HDL cholesterol is supported by a significant positive correlation between maximal aerobic work capacity and HDL-cholesterol levels in a group of 3,900 healthy women aged 18 to 61 years.[76] Likewise, total reported energy expended in leisure-time physical activity was not significantly related to HDL-cholesterol levels in women sampled in the Minnesota heart survey, whereas heavy-intensity work—6.0 kcal per minute or more—was significantly correlated with increasing HDL-cholesterol levels.[77] In contrast, significant positive correlations were found between both activity scores and HDL-cholesterol levels in men. Further study is indicated to delineate the effects of both physical activity and exercise training in men and women with respect to the mechanisms of coronary artery disease risk reduction (including plasma lipids and lipoproteins, blood pressure, obesity, fibrinolysis, and platelet adhesion).[78]

Psychosocial and Personality

Psychosocial differences may play an important role in affecting sex differences in heart disease risk. Male-female differences in health practices that are related to coronary artery disease have also been shown to be possibly related to psychosocial differences.[79] Among 3,516 men and women aged 30 to 69 years, a higher percentage of men than women smoked cigarettes.

The notion of "stress" has been widely popularized by the lay press as causative of coronary artery disease. The terminology in the area of stress and psychosocial behavior, once somewhat nebulous, is being more clearly defined. While doubt has been recently cast on the relationship of type A behavior with heart disease risk,[80] a cautious interpretation of this study is quick to point out that it is likely that certain components of the type A personality, rather than type A behavior as a whole, are related to the risk.[81] The type A behavior pattern, which represents a cluster of behavior traits, including hostility, aggressiveness and anger that are strongly suppressed, tenseness, hyperalertness, explosive speech style, impatience, and a continuous sense of time urgency, has been shown to be positively related to the risk of coronary artery disease in women.[21,82,83]

In the Framingham study, employed persons of both sexes tended to have a higher incidence of type A behavior than did their nonemployed counterparts. The incidence of type A behavior was most prevalent in older employed women and younger housewife subgroups.[82] For both women with jobs and housewives, however, type A behavior did represent an increased risk for coronary artery disease. While employed women tend to show more type A characteristics than their unemployed counterparts, this tendency is particularly prevalent between the ages of 30 and 35 years.[84] The peak in type A scores in employed women between the ages of 30 and 35 years is not noted in men and is attributed to the belief that type A women are less likely to leave their jobs when they have children. The Framingham study has shown type A behavior to be related to psychosocial states that may explain the relationship of this behavior pattern to disease risk: daily stress, emotional lability, tension, anger symptoms, and ambition.[85] The prevalence of these psychosocial factors appeared to diminish with age. Examination of the relationship of the prevalence of these factors to employment indicates a similar prevalence of psychosocial factors between employed women and men, but not between employed women and housewives.

Women with jobs—including both white- and blue-collar—were subclassified as clerical or nonclerical workers. Clerical workers were found to have an increased incidence of coronary artery disease.[86] In addition, the incidence of the disease in women increased with an increasing number of children. The incidence of disease was highest for clerical women whose husbands had blue-collar jobs. These findings suggest that the excessive risk in clerical workers with husbands in blue-collar jobs and children may be related to the stresses of economic pressures coupled with low job mobility.[82]

Sex differences in coronary artery disease risk as they relate to personality and psychosocial factors are also present in a study of cynomolgus macaques. A dominant social status in female monkeys is associated with less atherosclerosis than is noted in either dominant or subordinate male macaques and subordinate females.[87,88] Compared with subordinate females, the dominant group had regular ovarian function and relatively smaller adrenal glands, indicating they experienced less social stress. Because levels of plasma lipids and lipoproteins were similar between dominant and subordinate females, it appears the "female protection" from atherosclerosis enjoyed by the dominant monkeys occurred independently of changes in characteristics of plasma lipoproteins.

Although stress reduction and a decrease in coronary artery disease events has been shown in patients who have had a myocardial infarction,[89] the role of behavior modification as a primary intervention tool with respect to disease risk has not been clearly established. Further work is needed to clarify the importance of psychosocial and behavioral effects on the risk for both men and women and to characterize differences in sex responses. In addition, the role of primary intervention in stress reduction or disease risk modification needs to be firmly established.

Pregnancy

Is the most important event in many women's lives a coronary artery disease risk factor? While women are protected during their reproductive years, there is theoretic evidence to suggest that changes in plasma lipid and lipoprotein levels that occur during pregnancy can increase their risk.[90] Plasma levels of total cholesterol and triglycerides increase from prepregnancy levels during gestation. These increased plasma lipids return to prepregnancy levels after gestation. Although plasma HDL-cholesterol levels increase during gestation, they tend to drop below pregestational levels in the postpregnancy state.

Some epidemiologic studies have shown an increased risk of coronary artery disease with parity.[91,92] Others, however, reveal no significant increased risk of coronary artery disease events with the number of pregnancies.[93,94] The Nurses' Health Study, which included 119,963 female participants over a six-year period, found no relationship of myocardial

infarction incidence to an increased number of births or age at first birth when adjusted for risk factors.[95] Further work in this area is important to elucidate the relationship of hormonal events occurring during gestation with their influence on coronary risk factors in women. The application of work of this nature could extend beyond the pregnant condition to provide enlightenment on biologic events related to female protection.

Coronary Artery Bypass Operation and Angioplasty

Invasive therapy exists for both men and women who have shown coronary artery obstruction. Women without evidence of a myocardial infarction who are undergoing a coronary artery bypass operation generally have better left ventricular function compared with men.[96] Operative success, however, is less favorable for women than for men in terms of a higher operative mortality.[96,97] This is likely due to the smaller size of the coronary arteries in women related to less body surface area. In addition, women have other associated medical problems, particularly diabetes mellitus, that render coronary artery bypass procedures more technically difficult.[96] Despite these sex differences in perioperative mortality, postoperative long-term survival is similar in men and women. Similarly, percutaneous transluminal coronary angioplasty procedures are less successful and have a higher mortality in women than in men.[98]

Conclusions

Coronary artery disease represents a major cause of morbidity and mortality in women. Most of the investigation involving its risk factors has involved male subjects. Female subjects need to be the focus of future research, not only because of their risk of heart disease, but also because of unique female risk factors such as oral contraceptive use. In addition, further study is needed to clarify how behavioral and physical activity mechanistically affect the risk of the disease in women.

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* * *

There is more difference within the sexes than between them.

Ivy Compton-Burnett

Women and Medicine

Careers of Women Physicians
Choices and Constraints

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During the past 20 years there has been a striking demographic shift in American medicine. After a half century of constituting 5% of the physician population, women will soon make up nearly a third of American physicians. Women now practice in virtually every medical specialty. This enormous change has created both opportunities and tensions. Individual preferences combine with social and cultural incentives and constraints to determine the career choices of women physicians. Within the broader context of the changing role of women in American society, women physicians are exploring new career paths—paths that are both similar to and different from those of their male colleagues. We review the literature about women physicians in an effort to understand how they are responding to the current environment.

Career Choices

Demographics

The magnitude of change in the number of women physicians is remarkable. In 1985 there were 74,774 practicing women physicians, 14.6% of the total physician population and more than triple the 22,011 practicing in 1970. While this partly reflects a gradual increase in the total physician population from 312,047 in 1970 to 511,090 in 1985, an annual growth rate of 4.3%, the average annual increase in the number of women physicians was nearly quadruple the overall rate—16%. Even these numbers slightly underestimate the magnitude of the change because they do not include medical students.[1]

Medicine is an increasingly attractive profession for women. The percentage of women college graduates applying to medical school has tripled since 1970, going from 0.8% to the current rate of 2.3%. At the same time, there has been a drop from 4.9% to 4.2% in the percentage of male college graduates applying to medical school. Although this rapid growth appears to have recently plateaued, women now represent an unprecedented 31% of medical school students.[1]

Specialty Choice

The careers of women physicians do not mirror precisely those of their male colleagues. Among practicing women physicians in 1985, 68% worked in primary care fields: internal medicine, family and general practice, obstetrics and gynecology, pediatrics, or psychiatry. In contrast, only 44% of male physicians practiced in these specialties.[2] Such differences are likely to persist into the future because 69% of female and 50% of male residents entered primary care fields in 1985.[3] Furthermore, responses to a 1987 American Association of Medical Colleges questionnaire sent to graduating medical students indicated that 68% of women and 48% of men planned to enter primary care fields.[4]

Pediatrics and obstetrics and gynecology were especially attractive to women residents. Although women constituted 26% of all trainees in 1985, they filled 49% of residency positions in pediatrics and 42% in obstetrics and gynecology. Other fields with disproportionately high percentages of women residents included dermatology (40%), psychiatry (38%), and pathology (36%).[3]

Few women enter surgical fields. The number of women surgeons has increased only slightly since 1967, growing from 1.5% to 2.5% of all general surgeons in 1985. This slow increase is likely to peak at 5%, because data from 1985 residency programs showed that roughly 5% of surgical residents are women. Data for 1987 graduates also indicated that only 3% of women planned to enter general surgery, while an additional 7% planned to enter other surgical subspecialties. This aggregate percentage of 10% of women students interested in surgical fields remains unchanged from 1980 data from the American Association of Medical Colleges. Men consistently showed more interest in surgery, with about a quarter of fourth-year students planning to enter surgical fields. More than 95% of surgical trainees and practitioners are men.[2-4]

Not all students receive a residency position in their preferred—matched—specialty. Data from the National Resident Matching Program show that there is a difference be-

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tween men and women in the percentage of unmatched students in many specialties. For example, despite the paucity of women in surgery, about 25% of women applicants to general surgery residency programs failed to match, in contrast to about 15% of men applicants. In obstetrics and gynecology, pediatrics, pathology, and psychiatry—fields that have higher proportions of women trainees—women were also more likely to remain unmatched. In contrast, in both internal medicine and family practice, men more commonly remained unmatched. Because there are no comparative data on the quality of applicants, this information needs to be interpreted cautiously. Further research may help to determine if sex is an independent variable in the resident selection process.[5]

Practice Setting and Productivity

The gender differences in physicians' careers extend beyond specialty to choice of practice setting. Women physicians are less likely to be self-employed than men, with data from 1986 showing that only 52% of women physicians were self-employed, in contrast to 77% of men. The tendency of women to enter primary care fields that offer a greater number of employee positions does not fully explain this discrepancy; it extends to every field (except anesthesiology), including those with low percentages of physician employees.[6]

The difference between male and female physicians' productivity, measured in hours worked per year and number of patients seen, is decreasing. Currently there is no difference by physicians' sex in the number of weeks worked per year.[7,8] Although women physicians average less hours of work per week than men—52.5 versus 58.2—recent trends show a convergence, with women working more hours and men working fewer hours than in the past.[6] Women physicians see more new patients than their male colleagues and average longer visits per patient,[2,9] which, combined with their fewer hours of work per week, help explain why women physicians see fewer patients per week (99.3 versus 120.3).[2]

Economics

Discrepancies in income are only partially explained by data on specialty choice, practice setting, and productivity. In a 1986 American Medical Association survey, women physicians averaged $73,100 annual net income compared with $118,000 for men.[2] Every specialty and age category examined had a gender difference in income. Expressed as income per patient visit or income per hour, male physicians still received a higher income than female physicians at every stage of their career.[6] Three different sophisticated analyses using data from 1973, 1977, and 1982, respectively, found that employee status, specialty, age, number of hours worked, and number of patients seen accounted for only between 76% and 88% of the income differential.[10-12] This difference in income may be magnified over time by a difference in debt burden. Female students graduating in 1987 had an average debt of $37,732, which was $3,000 more than that of the average male student.[4] For at least the past 15 years, women physicians have not received equal pay for equal work.

Power and Promotion

Women are also underrepresented in positions of power. They are less likely than men to have positions of authority within professional organizations and academic medicine. Their tendency not to join medical organizations may partly explain why there are fewer women in powerful positions of organized medical societies. For example, in 1985 only 28% of women joined the American Medical Association, in contrast to 45% of men physicians.[13] This, however, cannot explain the paucity of women in senior academic administrative positions. Since at least the 1960s, women have been more likely than men to enter academic medicine. Yet, in the 1975-1976 academic year there were no women deans of medical schools, and women made up only 3.4% of associate deans and 11.7% of the assistant deans. Although these figures have improved somewhat, in the 1986-1987 academic year, only 1.6% of all medical school deans, 9.6% of associate deans, and 20% of assistant deans were women. In 1987 women chaired less than 5% of medical school departments in both the basic and clinical sciences, with a total of 29 chairwomen in the basic sciences and 44 chairwomen in the clinical sciences.[14,15]

These data reflect the difficulty women have in achieving promotion and tenure within academia. Data from the Faculty Roster System of the American Association of Medical Colleges reveal that among women medical school faculty first appointed in 1976, 21.7% were not on the tenure track, compared with only 15.4% of men. Of the full-time academic physicians on the tenure track, 16.6% of men had achieved tenure, whereas only 11.5% of women were tenured.[14,15] Moreover, a study of academic promotion patterns at four United States medical schools showed that at each school the average number of years to promotion for each faculty rank was consistently greater for women.[16]

Constraints on Careers

Clearly the careers female physicians pursue are different from those of their male colleagues. This reflects the complex influences on women seeking to establish professional lives that integrate diverse, and at times conflicting, roles. Men and women are expected to fulfill different roles within our society. One major locus of these different social expectations is family life and domestic responsibilities. Women who elect to enter any profession have faced, and continue to face, expectations that they will continue to fulfill a traditional role. This dual burden has affected women physicians for more than a century and continues to shape their career choices.

The social world of men and women physicians clearly reflects these differing expectations. About two thirds of women physicians were married, in contrast to the national average of approximately 90% of female nonphysicians and roughly 90% of male physicians. The divorce rate for women physicians was roughly 10%, considerably lower than the national average but approximately double that of male physicians.[17-22] These differences in family structure extended to parenting. Among male physicians who were married, 90% had children, in contrast to 60% to 70% of married women physicians. There was a suggestion that women physicians not only had fewer children but also were older when they had their children.[17-23] These differences are especially interesting because at the end of medical school, between 85% and 90% of both men and women stated that they wanted to have children.[23,24]

Men and women physicians have different roles in managing family and household responsibilities. This is partly

because the spouses of women physicians are more likely to be from an equivalent socioeconomic status. In one study, 70% of women physicians' husbands had received graduate degrees, in contrast to 30% of the wives of male physicians. This, combined with social norms, resulted in 95% to 99% of husbands of women physicians working outside the home, regardless of whether the couple had children or not. In contrast, 70% of childless male physicians' wives were employed outside the home. When male physicians had children, however, this changed dramatically, with nearly 75% of their wives not employed outside the home.[19]

Not surprisingly, child-care data reflect these facts. Women physicians relied on full-time household help, day care, and relatives to provide child care, with husbands the major source of child care in 0% to 5% of women physicians' marriages. In contrast, 50% of the wives of male physicians provided full-time child care, with an additional 33% providing a major contribution.[19,25] In a separate study, 75% of women physicians surveyed stated that they personally were responsible for most housework in their homes.[26] Clearly women physicians have the major responsibility for their family and household care.

These social expectations create tensions between the private and professional lives of women physicians. Such tensions can be exacerbated by health care professionals' negative attitudes towards maternal employment. Nearly 50% of male medical students and physicians in a 1982 study agreed with the statement that "women physicians who spend long hours at work are neglecting their responsibilities to home and family."[27] A 1983 study found 30% of responding physicians felt that there was "a significant risk to the optimal functioning of a department that hired a female of childbearing age."[28] A 1984 study found between 10% and 20% of nurses and physicians surveyed held strongly negative attitudes towards maternal employment.[29]

Social assumptions about appropriate roles help shape the careers of women physicians. When surveyed, between 30% and 60% of women physicians felt that family-career conflicts were important influences on their lives.[18,25,30] Even more telling was a survey that asked men and women if they changed their career plans because of family influences. None of the men said they had changed their career plans or behaviors because of family responsibilities, whereas 44% of the women said they had changed their plans in response to these issues.[25] A different study found that women explicitly sought regular and shorter working hours because of concerns regarding family life.[30]

One plausible interpretation of these data is that women physicians design careers that help them balance conflicting demands. Choosing primary care fields, employee status, and shorter working hours may allow an easier integration of personal and career roles. Although other factors undoubtedly also influence women's career choices, efforts to alleviate role conflicts appear especially important in their career decisions.

Conclusion

The relative contributions of personal choice and social constraints in influencing career decisions of women physicians are not known. Unfortunately, the structure of medical training and professional advancement inhibits or even penalizes persons who seek to devote substantial time to personal commitments. Although these issues are not inherently limited to women, they are especially important and poignant to women physicians because our society continues to place a disproportionate emphasis on women's domestic responsibilities. The logical response of many women physicians is to seek careers that are more amenable to integrating their personal and professional lives.

The influx of women into medicine provides an opportunity for the profession to examine its traditional ethic of professional responsibility to the exclusion of all else. There is an emerging consensus that many flaws in medicine—from unsympathetic patient care to substance abuse—may result from this impossibly demanding philosophy. Structural reforms within medicine, such as new promotion and tenure policies or shared residency programs, are needed to ensure adequate flexibility for both men and women to simultaneously pursue personal and professional development.

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Medical Women of the West

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The presence in the West of women physicians with degrees from regular medical schools spans a period of approximately 130 years. Women's Medical College of Pennsylvania graduated many of these early women physicians. The first woman medical graduate of a western school was Lucy M. Field Wanzer, who finished in 1876 at the Department of Medicine, University of California in San Francisco. Soon thereafter, schools that would become Stanford University and the Oregon Health Sciences University schools of medicine, as well as the newly founded University of Southern California, were contributing to the pool of women physicians. The University of Michigan Medical School, the first coeducational state medical school, also educated some of the western women physicians, who by 1910 numbered about 155.

This regional account of the progress of women physicians as they strove to become an integral part of the profession emphasizes the familiar themes of altruism, ingenuity, and perseverance that characterized their efforts.

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Women graduates of regular, as opposed to homeopathic and eclectic, medical schools were practicing medicine on the West Coast within 30 years of 1849 when Elizabeth Blackwell, the first woman to receive a medical degree in the United States, graduated at Geneva (New York) Medical College.

Simultaneous social movements and events—the founding of the suffrage movement in 1848, the California gold rush of 1849, and the opening of the Female Medical College of Pennsylvania, founded in Philadelphia in 1850 by men who were Quakers—each played a role in facilitating the entrance of women into the professional world. The drama and melodrama associated with the quest of women for a place in medicine provide endless material for those who would take up the pen.

The theme of service, the natural extension of the historic function of women, and their unique identification with the childbearing and child-rearing aspects of life motivated them to become physicians. They had long been midwives and nurses—the care givers—to women, children, and the elderly in their families and communities. Public health and preventive medicine were logical associated interests. Once the formidable barriers to medical school admission had been surmounted, women discovered the scientific attractions of medicine.

The contributions of women homeopaths and eclectics should be acknowledged. Although the quality of their practices varied greatly, their motivation to serve as medical practitioners was real. Women were welcomed into homeopathic and eclectic schools when doors were closed to them at regular medical schools.

The perseverance of women in establishing their own medical schools when admission was denied them elsewhere, in setting up their own dispensaries, clinics, and hospitals to provide practical training for themselves, in founding nursing schools, and in pushing their way into the medical societies is a fascinating saga. Their families, mentors, supporting friendships, and their community allies were critical ingredients in their success.

The first woman to practice in California is generally agreed to have been Elizer Pfeifer Stone (1819-1880), a German-born and -educated obstetrician who had practiced in New York. She arrived with her husband in Nevada City, California, in 1857 and located in San Francisco six years later. The specifics of her credentials are in doubt—it is unclear whether she attended or was a diplomate of a German medical school. Dr Rebecca A. Howard (1828-1896) arrived in San Francisco in 1864 after training in Philadelphia. She would later have a daughter, Kate, who would graduate in medicine in 1885 from the Toland Medical College, later to become the University of California, San Francisco, School of Medicine. Euthanasia S. Meade (1836-1895), whose given name assures her inclusion in any record of the era, and who was an 1869 graduate of Women's Medical College of Pennsylvania, came in the same year. Dr Charlotte Blake Brown (1846-1904), an 1874 graduate of what is now known as the Medical College of Pennsylvania,* had the distinction of being a resident of California who traveled East for a medical education. Her family had moved to California in 1851 from Philadelphia, crossing the Isthmus of Panama. Her father, a minister, established a boys' school in Benicia, California. Later assignments took the family to Chile and by

*1850, Female Medical College of Pennsylvania; 1867, the Women's Medical College of Pennsylvania; 1970, the Medical College of Pennsylvania.

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chance to Tahiti. These experiences instilled a missionary zeal in Charlotte Brown that was to last a lifetime. She returned to New England, graduated from Elmira College in New York, married, and settled with her husband in Napa, California. After having three children and reading medicine with her preceptor, Dr Charles Nichols, she chose to seek a medical education in Philadelphia. Her second year was spent as a hospital intern. This firsthand experience taught her the value of practical training. With Dr Martha Bucknall and Dr Sarah E. Browne, she founded the Pacific Dispensary for Women and Children in San Francisco, which was renamed and incorporated in 1885 as Children's Hospital and Training School for Nurses. This latter institution, which flourishes today, was the first hospital in the West to offer internships and residency training to women.

Dr Elizabeth A. Follansbee (1839-1917), a Massachusetts native, was a school teacher and friend of Dr Charlotte Brown in Napa, and she followed Brown's path to Philadelphia. En route she had studied at the University of California, San Francisco, and at the University of Michigan, Ann Arbor, which was the first state school to accept women medical students. She settled in Los Angeles, became the first woman in the West to have an academic appointment, and chaired the Department of Pediatrics at the University of Southern California.

By 1876, the School of Medicine of the University of California, San Francisco, had graduated its first woman, Lucy M. Field Wanzer (1841-1933), a 33-year-old school teacher, who was intellectually and emotionally able to cope with the hazing she received. She was thus the first woman graduate of a western medical school. The Medical School of the Pacific (later Stanford University School of Medicine) graduated Alice Higgins in 1877 and Anabel McG. Stuart in 1878. Western state medical schools were coeducational from the beginning, but the University of California had to be reminded of this by its regents when Lucy Wanzer and another female applicant were at first denied admission.

Other western medical schools were now also admitting women students. The sisters Angela L. and Ellen A. J. Ford graduated in 1877 from the Willamette University, Salem, Oregon (later the University of Oregon Medical School and since 1974 the Oregon Health Sciences University School of Medicine, Portland). The first class to graduate from the Medical Department of the University of Southern California included one woman, Lula Talbot. The year was 1888.

In a sequestered society in Utah, Mormon women of intellectual promise were being encouraged to study medicine by Brigham Young. Earlier there had been a mistrust of the medical profession by this religious sect. Midwifery had been an important assignment for women because of the many children born during the early period of colonization. Women saw the need but had difficulty responding to the call in the middle of their own childbearing years. Two women, first Romania Bunnell Pratt-Penrose (1839-1932), followed by Mary Ellis Reynolds Shipp (1847-1939), matriculated at Women's Medical College of Pennsylvania in the 1870s. They returned to Utah to practice obstetrics, pediatrics, and public health. Nurses' training and instruction were also a part of their activities. They both lived to be older than 90 years and were revered by their communities.

Dr Bethenia Owens-Adair (1840-1926) was the first female regular physician to practice medicine in Oregon. Born in Missouri, she moved westward in a covered wagon in infancy, taught school, attended an eclectic school in Philadelphia in 1873, practiced a few years, and then enrolled in the University of Michigan School of Medicine from which she graduated in 1880 at the age of 40. She was prominent in several sections of Oregon, promoting woman's suffrage and eugenics.

Dr Maria M. Dean (1858-1919), a University of Wisconsin undergraduate, obtained an MD degree from Boston University School of Medicine in 1883 and became the first woman to practice in the Montana Territory. She had a large practice among women and children and was the first woman to read a paper before the Montana Medical Society, "Typhoid Fever in Infants." As was usual for women physicians, she was active in community affairs. She was identified with the Board of Education, the Young Women's Christian Association, and as an advocate of improved working conditions for women.

Dr Helen C. Roberts (1861-1931), the first woman to be an intern at Cook County Hospital in Chicago, practiced for 32 years in Great Falls, Montana.

Dr Mary Babcock Moore Atwater (1858-1941), an early force behind the establishment of the State Tuberculosis Hospital at Galen, Montana, started her career in this state by being the physician for the Gold Leaf Mining Company, making her rounds on horseback over narrow mountain trails.

Chloe Annette Buckel (1833-1912), another graduate of Women's Medical College of Pennsylvania, settled in Oakland, California, in 1877. Her medical peregrinations following graduation in 1858 included association with Doctors Elizabeth and Emily Blackwell in New York, heading an army nurses' service during the Civil War, working for 12 years with Dr Marie Zakrzewska in the New England Hospital at Boston, and studying for 2 years in Europe. In California she was largely responsible for the certification of milk by the state.

In 1876, after the passage of the Medical Practice Act, and not without much deliberation, five women physicians were admitted to the California State Medical Society at its San Francisco convention. Women gradually gained acceptance into the county medical societies; Lucy Wanzer became a member of the San Francisco Medical Society in 1877. Dr Mary McGill soon followed, joining the Sacramento society. Women were never prominent office holders in the early years, with the exception of Dr Charlotte Le Breton Johnson Baker (1855-1937), a Cooper College (later Stanford) graduate of 1890, who was President of the San Diego County Medical Society in 1898. Other offices were filled by women as well, which situation was often called a "gynecratic complication." Rose Talbot Bullard (1864-1915) was the one and only woman president of the Los Angeles County Medical Association (from 1903 to 1904).

These historical notes do not presume to be inclusive but rather are an attempt to capture some of the color and ardor of those times and persons.

By 1910 it was estimated that regular medical women numbered 155 in the West (5% of that category of physicians), women homeopaths 90 (15% of that group), and eclectics 45 (10% of that total). This may have reflected the national proportions at that time.

American Medical Association data show a total of 90,750 women physicians in the United States in 1987, 15.7% of the total number of persons with an MD degree.

These numbers foretell the entirely different story that will be written about medical women in the 21st century.

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Thoreau, New Mexico, Feb 20, 1920

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Women and Medicine

Diagnostic and Treatment Challenges

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Recurrent Urinary Tract Infections

OF THE MANY gynecologic and hormonal health problems that cause women discomfort and concern, none is more easily managed than recurrent urinary tract infections. Of all recurrences, 99% or more are reinfections—that is, each infection is caused by a new and different organism from the rectal reservoir of bacteria. Recognition of this reservoir, and the fact that each infecting strain must first colonize the vaginal mucosa before it enters the bladder, has major consequences for both diagnosis and treatment.

To accurately diagnose the presence of bacteria in the bladder urine, contaminating pathogenic organisms on the vaginal and urethral mucosa must be avoided. This task is accomplished most accurately by doing a suprapubic needle aspiration of a full bladder, almost as accurately by catheterizing the bladder—the bladder must be full and the specimen for culture collected only after several hundred milliliters of urine have washed out the contaminating urethral bacteria—and much less accurately by separating the patient's labia and collecting, under direct vision, a late voided specimen from a full bladder. With the first two techniques, the presence of any number of bacteria is diagnostic of an infection; with the last technique, 1,000 or more bacteria per milliliter should indicate an infection within the bladder. The presence of many leukocytes per high-power field in a centrifuged urine aliquot can be confirmatory.

Colonization of the vaginal mucosa by rectal bacteria has equally major consequences for treatment. There are several effective regimens, all of which depend on the biologic principle that an oral antimicrobial agent must not carry a high risk of altering the lower rectal bacterial reservoir and especially should not induce resistance. The most useful agents are trimethoprim-sulfamethoxazole, nitrofurantoin, cephalexin, and cinoxacin, all used in prophylactic dosages of a quarter to half of a standard-sized tablet. The smaller the dose, the less the adverse effect on the rectal reservoir. Successful prophylactic strategies include a single, small, postintercourse dosage for sexually active women, including—at least for nitrofurantoin and cephalexin—reinfections during pregnancy; nightly bedtime prophylaxis for very sexually active women; and even thrice-a-week bedtime prophylaxis. All of these work well. A fourth, and very effective, nonprophylactic regimen is to wait and treat each infection at the first sign of recurrent symptoms; full-dosage therapy for three days is more than adequate with any of these four drugs. For a patient who has three or fewer infections per year, this fourth regimen is the most desirable and acceptable to women. They must be allowed, however, to have the antibacterial agent on hand and to institute their own therapy without benefit of an office visit; if their symptoms persist for longer than five or six days, an office visit is appropriate. For a sexually active woman with more than three infections per year, postintercourse prophylaxis is the most effective with the least amount of drug. For a woman or child with reinfections who is not sexually active, bedtime prophylaxis on a nightly or thrice-a-week regimen is usually required.

Before considering those rare cases of women who have more serious infections, physicians should remember that a diagnosis of urinary tract infection cannot be established by symptoms alone; indeed, 27% to 34% of women thought to have acute cystitis will have sterile urine on urethral catheterization—the so-called urethral syndrome about which so little is known—but vaginitis caused by *Candida* or *Trichomonas* should also be ruled out by examining under a microscope a wet vaginal smear. It should also be recognized that pyuria—five or more leukocytes per high-power field in a centrifuged specimen—occurs in only 50% of asymptomatic women with a urinary tract infection, and that pyuria can occur without infections in several diseases of the urinary tract such as interstitial cystitis and in situ carcinoma of the bladder. Thus, it is difficult to rely exclusively on urinalysis for the diagnosis of urinary tract infection. Interestingly, however, there is no solid evidence that asymptomatic urinary tract infections need to be treated except during childhood and pregnancy. There is clearly no reason to treat asymptomatic infections in the elderly or in patients with an indwelling urethral catheter. If symptoms occur in a catheterized patient, especially fever, therapy for a few days is warranted, but continuous antimicrobial treatment is wasted and simply insures infection with multiply resistant bacteria.

Most female patients with recurrent pyelonephritis, including children younger than 2 years, also have ascending reinfections of their urinary tract; they should probably be treated for seven to ten days rather than the three-day regimen described above for recurrent cystitis. To be sure, a few female patients with recurrent infections are at an increased risk of renal damage or at least severe morbidity, and their cases should be recognized and treated with special care. These patients include children younger than 2 years with severe ureteral reflux (all recurrences are reinfections, however); women with recurrent *Proteus mirabilis* urinary infections in whom the urea-splitting bacteria have caused a struvite renal stone to form; women with renal papillary necrosis due to diabetes mellitus or analgesic abuse who may have high-pressure obstruction of their ureters, causing severe renal damage; women with spinal cord injury with an associ-

ated high-pressure obstruction of the bladder from pelvic floor spasms; women with diabetes who have chills, fever, flank pain, and emphysematous pyelonephritis (diagnosed by finding intraparenchymal or perirenal gas on a plain film of the abdomen), a disease that carries a 43% mortality without early diagnosis and surgical drainage; and, finally, women who have pyelonephritis in the last trimester of pregnancy, a condition easily prevented by the diagnosis of a urinary tract infection in the first trimester, treated for three days with curative oral antimicrobial therapy, and followed by post-intercourse prophylaxis with nitrofurantoin or cephalexin.

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Premenstrual Syndrome

ALTHOUGH IT WAS FIVE DECADES AGO that Frank first described the premenstrual syndrome in the medical literature, little progress has been made in our understanding of this condition. As a result, family, friends, and physicians have often rejected the idea that it is a medical disorder and accused women with premenstrual symptoms of a lack of character, sanity, or moral fiber. This situation is not surprising, however, for until recently there has not been a clear definition or set of diagnostic criteria, a convincing theory for its etiology, or a proven approach to the therapy for the premenstrual syndrome.

Fortunately, a renewed interest in this phenomenon in the early 1980s by the medical and popular press has led to a serious attempt by many medical and social scientists to unravel the mysteries of this enigmatic problem. The first major article written by medical researchers in this country in the 1980s was by Reid and Yen.[1] They stated their belief that the premenstrual syndrome was a psychoneuroendocrine disorder—that is, a condition resulting from a disturbance of the neuroendocrinologic system but greatly influenced by psychosocial factors. Based on animal studies that showed a premenstrual decline in β-endorphins in the hypophyseal portal system and the similarity of many premenstrual symptoms to those that accompany an exposure to and withdrawal from narcotics, they proposed that a withdrawal from endogenous opiates may incite premenstrual symptoms. Unfortunately, studies of circulating endorphins in women with and without premenstrual symptoms proved contradictory. In the minds of many, however, their article legitimized the premenstrual syndrome as a medical disorder and stimulated the search for a common biochemical defect or a biological marker for the condition, a search that has not yet been successful.

While failure to discover a biochemical defect or biochemical marker has convinced some that the premenstrual syndrome is not a medical diagnosis at all, this failure probably reflects more our limited understanding of psychoneuroendocrinology and the limitations of our investigative tools and techniques than the nature of the syndrome.

Another problem facing clinicians and researchers had been the absence of a universally accepted set of diagnostic criteria. The 1980s, however, also produced a landmark article by Rubinow and Roy-Byrne that critically analyzed the methods of the past, established guidelines, and set standards for designing valid and reproducible studies.[2] Consequently, recent published studies of the premenstrual syndrome have been of higher quality and more believable than at any time in the past. As a result, many skeptical physicians are now taking an active interest in this issue. They recognize that distressing symptoms begin about 2 weeks before the menses and end within 24 hours after the menses begin. The most common physical symptoms are fatigue, headache, abdominal bloating, breast tenderness and swelling, and acne. Anxiety, hostility or anger, and depression occur in more than 94% of women with the syndrome. Many have psychological reactions such as guilt, decreased self-esteem, and shame; many also report notably disturbed family and work lives.

Another encouraging development has been the improved communication that has occurred between the psychologically oriented "camp" and the biologically oriented one of investigators and clinicians.[3] Whereas each camp previously gave lip service to the other, now each borrows concepts and methods from the other. Realizing that the premenstrual syndrome most likely is the result of both external (social) and internal (psychobiologic) factors, multidisciplinary teams have been formed to study, evaluate, and treat women with the disorder. This cooperation has led to new and effective treatment approaches, including various combinations of education, medication, and counseling—peer, individual, group, family, and marital. It now appears that a biopsychosocial model of the syndrome has come of age.[4]

Despite these dramatic advances in the field of "PMS-ology," we still have a long way to go. Scientists and health care providers, however, can be excited about the rapid rate at which insight into the nature of the syndrome is being gained. Most important, women with the disorder can be increasingly optimistic that in the future their care will be even more compassionate and effective.

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Advances in the Diagnosis and Treatment of Ovarian Cancer

OVARIAN CANCER is responsible for the death of more American women than cancers of the uterine cervix and corpus combined. It has been estimated that 19,000 new cases of ovarian cancer will be diagnosed in 1988 and that 12,000 of these women will eventually die of their disease.

Approximately 70% of all patients with epithelial ovarian cancer present with disease that has already spread beyond the confines of the pelvis to involve peritoneal sites throughout the abdomen. The role of aggressive cytoreductive surgery in the management of these patients remains

controversial. Several reports have now confirmed that patients with residual disease measuring less than 2 cm exhibit a higher rate of complete remission and a longer duration of survival than patients with bulky residual masses. Those who question the value of an aggressive surgical approach argue that a fundamental difference in tumor biology is responsible for the unfavorable prognosis in patients with bulky residual masses.

The resection of bulky abdominal disease poses a formidable challenge even to the most experienced and skillful surgeon. For this reason, it has been possible to achieve "optimal" cytoreduction in no more than 40% to 70% of cases. The results of a recent study offer some hope of improving these figures. In nine of ten elderly patients, an ultrasonic surgical aspirator was used to achieve cytoreduction of bulky peritoneal metastases to less than 0.5 cm. Procedures involving the aspirator took less than half the time required for conventional surgical techniques. Bowel resection was avoided in all but one patient, and no operative complications were attributed to the use of the device.

For many years, the primary focus of research in ovarian cancer has been the development of a more effective chemotherapeutic regimen for patients with advanced disease. Several prospective, randomized trials have now shown that the intravenous administration of cisplatin in combination with cyclophosphamide constitutes the most effective treatment for these patients. Chemotherapeutic regimens containing the two drugs have yielded objective response rates of 60% to 80%, complete response rates of 30% to 40%, and a median survival of 24 to 30 months. The addition of Adriamycin (doxorubicin hydrochloride) or other agents does not appear to enhance the effectiveness of the two-drug combination.

In patients with persistent disease at a second laparotomy, the likelihood of a response to additional intravenous chemotherapy is less than 20% and the median survival is only six months. Ovarian cancer, however, is uniquely suitable for an alternative approach to drug administration. The direct intraperitoneal instillation of a chemotherapeutic agent exposes residual tumor nodules to an extremely high drug concentration as compared with systemic levels, making it possible in theory to enhance the drug's therapeutic index. In a recent study of intraperitoneal chemotherapy for residual disease at a second laparotomy, a cisplatin-based combination yielded a median survival of more than four years in patients whose disease measured less than 2 cm. Unfortunately, patients with more extensive residual disease did not benefit to the same degree.

Localized ovarian cancer is usually asymptomatic. Until recently, the only potential screening test for asymptomatic disease was a vaginal examination. Discovery of the CA-125 antigen and improvements in the technique of real-time ultrasonography have raised the possibility that an effective program for early detection can be developed. The CA-125 antigen is a glycoprotein that is expressed by more than 80% of nonmucinous epithelial ovarian cancers. Real-time ultrasonography is an accurate method of measuring ovarian volume.

In a recent study to determine the feasibility and specificity of multimodal screening, serum CA-125 levels were determined in 1,010 postmenopausal women. Ovarian ultrasonography, a less specific and more expensive test, was carried out in the 30 women with CA-125 levels greater than 30 units per ml. Only three of these women with elevated CA-125 levels had abnormal ultrasound scans. One of them was found to have stage I ovarian cancer, while the other two proved to have benign pelvic abnormalities. The specificity of the multimodal screening program was therefore 99.8%. To determine whether such a screening program is of real value would first require additional studies to define the sensitivity in patients with localized disease. Ultimately, it would be necessary to do a randomized, controlled trial to show a reduction in mortality.

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Topical Retinoic Acid, Aging, and the Skin

AMERICANS ARE CONTINUALLY BARRAGED by commercial images that promote gnawing anxiety about the normal consequences of aging. A disproportionate share of this dissatisfaction has focused on the perceived ravages of aging on the skin and its appendages. Much of this attention has been useful; for example, an increased use of sunscreens should slow the alarming recent increase in cases of skin carcinoma and melanoma. On the other hand, much of the anxiety about aging is not endogenous but fueled by aggressive marketing targeted at a population evermore dependent on passively received, idealized images for its perception of normal. Whether this has been beneficial is certainly debatable, particularly if the price is despair and depression. Physicians, traditionally the last bastion of skepticism and independent thinking, likewise are becoming increasingly dependent on passively dispensed information—videocassettes, direct mail advertising, drug company-sponsored speakers, and throwaway journals compiled by nonmedical journalists—because they, too, are part of a society that reads and thinks less. By obtaining their information through these routes, physicians knowingly or unwittingly become salespeople, themselves extensions of a marketing network, corrupting their primary responsibility as patients' advocates.

Nevertheless, the phenomenon is upon us. Where before monarchs, poets, and commoners alike awaited their death knell from an early age with each serious illness, we can now reasonably expect longevity, while at the same time our skin will increasingly be besieged by the electromagnetic consequences of a careless disregard of a deteriorating atmosphere and increased sun exposure due to expanded leisure time and Sunbelt migration patterns.

A veritable smorgasbord of cutaneous offerings awaits those in search of the font of youth: body recontouring by removal (plastic surgery or liposuction), or augmentation (collagen, fat, or silicon implantation), hair-growth potions of still-unproven value, "cosmetics of the future," and topical retinoids. Although all of these approaches merit separate examination of their relative virtues and demerits, it seems

particularly timely to discuss topical retinoic acid (tretinoin; Retin-A) in view of the recent, carefully managed spate of publicity surrounding this agent.

Is there solid evidence for its usefulness? Can physicians delineate specific indications for its use? Retinoic acid, the progenitor of several generations of synthetic retinoids,[1] exerts powerful effects on epidermal differentiation. By normalizing keratinocyte maturation, this agent can reverse and prevent preneoplastic changes, but only a few established skin cancers respond to either systemic or topical retinoids.[2]

Although the driving force for the development of the synthetic retinoids is the excessive toxicity of vitamin A and its derivatives, ironically, it may be the low-grade irritancy of retinoic acid that promotes its percutaneous delivery to the dermis, allowing this agent to exert its effects on mesenchymal elements in that layer. By stimulating fibroplasia, leading to de novo collagen and proteoglycan synthesis, retinoic acid displaces downward actinically damaged, elastotic collagen.[3] In addition to its effects on keratinocytes and fibroblasts, topical retinoic acid apparently can stimulate endothelial cell proliferation and pigment dispersal,[4] effects that also can improve the appearance of photodamaged skin. Retinoic acid has been appreciated longest for its impact on pilosebaceous structures: in addition to diminishing sebum output, retinoic acid may reduce the number of open and closed comedones. The former, in particular, are an additional stigmatum of photodamaged skin. Finally, in altering epidermal differentiation and accelerating shedding, topical retinoic acid can reduce much of the excess scale that can be a concomitant of aging skin. In fact, retinoids remain the most effective form of therapy for the ichthyoses,[5] a broad group of inherited and acquired disorders characterized by excess scale.[6]

Is topical retinoic acid a panacea for photoaging? Certainly not. The impact on extensively damaged, deeply furrowed skin is minimal. But the ability of this agent to reverse and prevent epidermal neoplasias—albeit not as effectively as 5-fluorouracil; stimulate the renewal of various cellular elements in the dermis; promote normal pigmentation; and reduce both excessive scale and follicular cornified material makes this agent, and perhaps generations of topical retinoids still to come, reasonable therapy for extensively photodamaged skin. Finally, there are obvious advantages to medical versus surgical therapy for extensively sun-damaged skin, although the use of topical retinoids does not preclude, and even may complement, such surgical interventions as dermabrasion, chemical peels, and collagen implantation.

Topical retinoids also hold promise as primary and adjunctive therapy for a variety of other cutaneous processes, including enhancing the healing of leg ulcers in patients receiving systemic steroids or nonsteroidal anti-inflammatory agents, reversing dysplastic changes in dysplastic nevi, treating a variety of mucosal ulcerative and scarring conditions, and stimulating hair growth. Much of this work is still preliminary and beyond the scope of this article but available to readers in two recently published symposia.[7,8]

Finally, the use of topical retinoids mandates certain precautions. Retinoids are not only antineoplastic but also potentially tumor *promoters* in certain photocarcinogenesis assays.[9] This, plus phototoxicity due to possible retinoid-ultraviolet A interactions or a diminished generation of protein products of epidermal differentiation, can produce photosensitivity. Hence, the use of broad-spectrum sunscreens (a sun protective factor of 15 or higher) is indicated, which use will also help prevent a further progression of the deleterious effects of sunlight. Topical retinoic acid is also an irritant and therefore particularly difficult to administer to patients with "sensitive" skin—that is, those with atopy. Yet, with patience and careful follow-up, the poorly understood phenomenon of "hardening" occurs, allowing almost anyone to use this agent. Finally, the consequences of long-term usage in the elderly are not known, although some adolescents and young adults have used topical retinoic acid for decades without problems.

In the final analysis, it is the treating physician who must decide whether retinoids are indicated medically, cosmetically, or both—that is, when is one prescribing legitimately versus pandering to the wishes of patients simply shopping for the latest cosmetic angle. In the latter case, the risks may outweigh the potential benefits.

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Persistent Vaginitis

IN EVALUATING AND TREATING VAGINITIS and vaginal discharge, clinicians frequently face situations that are not straightforward.[1] Treatment choices often seem arbitrary, and failures occur. Confusion arises because of considerable variation in symptoms, coexistent infections, poor patient or partner compliance, and cultures that may not be specific.

Yeast Vaginitis

The organisms causing yeast vaginitis—*Candida albicans, Candida* species, and *Torulopsis glabrata*—can be identified in 10% to 30% of routine vaginal cultures because of high asymptomatic carrier rates.[2-4] Symptoms vary from minimal discomfort to intense itching or burning with associated vulvar erythema and abrasions. The vaginal discharge is scant to moderate, appears white and curdlike but may be thin and pasty, tends to adhere to vaginal walls, has no odor or smells musty, and has a pH of 4.0 to 5.0. A saline slide preparation shows a slight to a pronounced increase of leukocytes per high-power field. Adding potassium hydroxide shows mycelial forms. The highest yield will come from scrapings of vaginal sidewalls or the introitus.

The standard treatment of yeast vaginitis consists of applying miconazole or clotrimazole, 100 mg, to the vagina in

TABLE 1.—*Recommended Treatment for Persistent Vaginitis*

Type of Vaginitis	*Treatment Regimen*		*Recurrent or Refractory Infections*
	Initial Infection	*Recurrent Infections*	
Yeast infection	Miconazole or clotrimazole, 100 mg at bedtime × 7 vaginally, *or* 200 mg × 3	Prolong therapy over 2-3 menstrual cycles; apply gentian violet; apply acidifying agents (vinegar douches, Aci-Jel)	Treat partner topically; check for condylomata; give maintenance dose of ketoconazole; review risk factors (diabetes, oral contraceptive use, antibiotic therapy, immunosuppressive therapy)
Trichomonas vaginalis	2 grams metronidazole orally, treat partner	500 mg metronidazole orally bid × 7 d; review sexual contacts; recommend condom use	1 gram metronidazole orally × 7 d; 100 mg clotrimazole vaginally × 7 d; betadine douches
Bacterial vaginosis	500 mg metronidazole orally bid × 7 days; may be useful to treat partner	Metronidazole, same dosage as for initial infections; treat partner; recommend condom use	Check for coexistent infections; evaluate upper tract; apply acidifying agents
Atrophic vaginitis	2-4 grams estrogen cream every night for 1-3 weeks, ½ to 1 applicatorful; taper to once or twice a week	Estrogen cream, as for initial episode	Consider estrogen replacement therapy

bid = twice a day

cream or suppository form for seven nights or 200 mg for three nights (Table 1). The cream may also be applied directly to the labia and groin. Persistent symptoms occasionally require a second treatment course.

Those at increased risk for recurrent or refractory infection include women with diabetes mellitus; obese or pregnant women; women with an impaired immune response; and those receiving antibiotic therapy, oral contraceptives, or immunosuppressive agents.

In patients with refractory infections, the presence of the fungal agent should be documented by vaginal culture or potassium hydroxide slide. Sometimes a neurodermatitis, lichen simplex chronicus, develops as a sequela to severe yeast infections, and topical corticosteroids are needed to relieve the pruritus.[5] Coexistent infections may occur. Condylomata can cause persistent itching or dyspareunia and may be overlooked during an active yeast infection. The vulvar mucosa often displays only subtle findings with a cobblestoned or fine papillary pattern. A simple punch biopsy of the vulvar mucosa will confirm the diagnosis.

For patients with recurrent yeast infections, the following recommendations may be helpful:

- Extend the course of therapy through two to three menstrual cycles. Either try administering miconazole, 100 mg nightly, from the beginning of one period through the end of the next period, or have the patient apply 100 mg of miconazole to the vagina for ten nights during each of three menstrual periods in a row.
- Treat the patient's sexual partner topically with miconazole cream applied to the penis (especially prepuce) and groin twice a day for ten days.
- Treat the patient prophylactically whenever antibiotics are administered.
- Gentian violet applied directly to the cervix, vagina, labia, and perianal mucosa is surprisingly successful. For persistent infections, repeat the application once or twice at weekly intervals or just before the menses.
- Finally, Sobel has shown excellent results using oral ketoconazole, 200 mg daily for six months, as long-term suppressive therapy.[6] When using this drug, surveillance for potential hepatic toxicity is necessary.

Patients should also be instructed in proper genital and toilet hygiene. Keeping the area cool and dry is important, and all-cotton underwear, not merely cotton-crotch varieties, aids in absorbing natural moisture. Some women find remedies designed to boost vaginal acidity can reduce the frequency of yeast infections. These would include Aci-Jel (an acidifying vaginal gel) or vinegar douches (two to three tablespoons to a quart of warm water) once or twice a week.

Bacterial Vaginosis

Bacterial vaginosis (formerly nonspecific vaginitis) is a condition of anaerobic bacterial overgrowth associated with *Gardnerella vaginalis, Bacteroides* species, and the more recently identified *Mobiluncus* species.[7-9] Although associated with sexual activity, the etiologic agent has not been pinpointed. *Gardnerella* organisms can be identified in as many as 20% of specimens from asymptomatic women and are found in screening cultures.[10,11] Also, coexistent infections are common.

Patients with bacterial vaginosis often lack inflammatory response, and their predominant symptoms are discharge or odor. The discharge appears homogeneous, thin or pasty, and can be white, gray, or yellow. The pH is usually 5.0 or higher. The anaerobic bacteria produce organic acids that cause the foul odor. When a drop of potassium hydroxide is added to a laboratory specimen—the amine or sniff test—these acids are converted to volatile amines and a fishy odor can be detected. This odor is transient and can be missed, but patients may notice it when their discharge comes in contact with soap or semen. A saline slide preparation will show normal to moderately increased leukocyte counts per high-power field and the presence of "clue" cells, epithelial cells studded with bacteria having a granular appearance.

A seven-day course of metronidazole, 500 mg twice a day, is more effective than giving ampicillin or sulfa creams. Routinely treating the partner is a controversial though acceptable practice but is a logical next step if infection recurs.

Trichomoniasis

Trichomonas vaginalis is a sexually transmitted protozoan causing vaginitis in women. Men harbor the organism in the paraurethral glands and prostate but are usually asymptomatic. A symptomatic woman will present with a malodorous discharge that can be scant to profuse, yellow or green, watery, and sometimes frothy. The pH is greater than 4.5. The classic "strawberry cervix," mucosal microabscesses studding the cervix, is rarely seen. Adding potassium hydroxide to a specimen often produces a positive sniff test, and the saline slide shows a moderate to substantially in-

creased leukocyte count. The diagnosis is confirmed by identifying the motile forms on a fresh saline slide. The protozoans are readily recognized by their random motion and beating flagella.

Treatment consists of 2 grams of metronidazole taken orally in a single dose for the patient and partner. Treatment fails most commonly when there is reinfection. Reviewing condom usage and the patient's sexual contacts and retreating with metronidazole usually resolve the infection. True antibiotic resistance is rare, but in cases of partial resistance, treating a patient with metronidazole, 500 mg twice a day for seven days, is successful.

Noninfectious Vaginitis

Noninfectious causes of vulvovaginitis include reactions to a variety of chemicals: medicated douches, iatrogenic agents, spermicides and sponges, feminine deodorants, and harsh soaps. Foreign bodies are a notorious cause in children, but in menstruating women a forgotten tampon is not uncommon. Discontinuing the irritating chemical or removing the foreign body results in a clearing of symptoms.

Atrophic vaginitis affects postmenopausal women and is caused by thinning and weakening of the vulvar and vaginal tissues, a rise in pH accompanying a loss of the glycogen content, and a subsequent bacterial overgrowth. Treatment consists of applying estrogen cream, 2 to 4 grams daily—equivalent to a half to a full applicatorful—for one to three weeks. As soon as symptoms subside, treatment should be tapered to once or twice a week at minimal dosages because significant systemic absorption may occur and lead to endometrial stimulation. If local, vaginal treatment is inadequate, systemic estrogen replacement therapy may need to be considered.

Upper Genital Tract

When vaginal discharge persists and vaginitis has been excluded, an upper tract source should be considered. Uterine problems include endometritis, irritation caused by an intrauterine device, polyps, and malignancy. In cases of suspected cervicitis, cultures for *Chlamydia,* gonorrhea, and herpes simplex virus should be done. The Pap test, colposcopy, and cervical biopsy are invaluable techniques for identifying cervical condylomata, cervical dysplasia, and cervicitis.

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An Effective Clinical Approach to Vaginismus—Putting the Patient in Charge

VAGINISMUS is an involuntary spasm of the introital muscles in anticipation of vaginal penetration. Classically, its severest form makes penetration virtually impossible and causes a severe, burning pain. But there are less pronounced degrees of vaginismus, characterized by a "stiffening" of the vaginal musculature, allowing penetration, yet accompanied by the same sort of pain. The condition may be primary (present from the first attempt at penetration) or secondary (following physical or psychological trauma, infection, menopausal changes, or pelvic pathology).

Although the incidences of primary and severe vaginismus (prohibiting penetration) are relatively low, secondary vaginismus and introital "guarding" are seen reasonably frequently in clinical practice. Modern treatment methods approach 100% success, given the outcome criteria described by Kaplan. The technique detailed herein is a useful refinement.

The diagnosis of vaginismus can only be verified by physical examination and after other causes of local pain or atrophy have been treated or ruled out. These include the obvious and subtle causes of superficial dyspareunia, such as anatomic abnormalities, infections, mucosal tears, hypersensitive scars, atrophic vaginitis, inadequate lubrication, painful hymeneal tags, urethral caruncle, topical allergies, focal vulvitis, postherpetic neuralgia, and hypersensitivity to a partner's semen.

On physical examination, the patient is tense, the buttocks tight, the thighs adducted, and the perineum taut and contracted. The treatment is based on several prerequisites:

- The cause of the condition—determined by history—must be explained to the patient, as must its mechanics.
- The patient must be motivated to enjoy coitus or desire to effect painless vaginal insertion for other reasons—self-acceptance, the use of tampons, comfort during medical examinations.
- The patient must learn that she can be in control of her vagina at all times during treatment.
- The patient—and her partner—must be willing to patiently undergo a progressive process of systematic desensitization and counseling.

Treatment begins with the pelvic examination. The patient is assured that she is in control: When she says, "Stop," the examiner always stops. It may take several sessions to demonstrate painless vaginal insertion. The wait is worth it in the long run. The patient is taught the Kegel exercises, with special attention to bearing down and pulling in. When she can do this easily, the examiner (with the patient's permission) gently places the tip of the index finger at the introitus, asking the patient to bear down or "push the finger away." Repeating this exercise several to many times, with rest periods, should eventually result in the fingertip being "captured" by the vagina (as opposed to the vagina being "penetrated")—an active, rather than passive process. The patient comes to realize that she can be in active control of what enters her vagina and is usually astonished to discover that it is painless. Patience, gentleness, and time will permit the length of a finger to be "captured" in this way. The same procedure is repeated by the patient herself and, if possible, by her partner. Graduated vaginal dilators are substituted for the finger at home and are left in place for 15 to 60 minutes at

a time. Trust is developed as the patient teaches her partner how to cooperate. Finally, the exercises are incorporated into sexual situations, and the penis is substituted, under the patient's control, only when she is reasonably aroused. In the short run, the patient is always in control.

Clinicians should warn such patients to anticipate setbacks during the treatment process—in fact, should program them into the treatment. They should be aware that overcoming vaginismus may uncover other sexual dysfunction(s) that can be addressed subsequently without the barrier of dyspareunia.

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Contraception—Problems and Prospects

Assessing the present and future of fertility regulation in 1985, Diczfalusy observed that

> the most important problem with presently available fertility regulating methods is simply that people are not using them. . . . Out of approximately 600 million couples in the reproductive age [in developing countries], some 500 million are not using adequate methods of fertility regulation.

Needless to say, this problem weighs most heavily on women and has not been corrected in the three intervening years. It is not a problem unique to developing countries. The first federally funded family planning clinic in the United States was established 23 years ago in Corpus Christi, Texas. At that time, 5.3 million women in this country were estimated to be at or below the poverty level and in need of subsidized family planning services. Today 5 million women receive services annually; another 3.6 million, also in need, are not served.

The toll of unmet needs and of methods not used is starkly evident among very young women. Women 15 to 19 years old account for nearly a third of all unintended pregnancies in the US; three quarters of these pregnancies can be attributed to not using contraception. Less than half of all sexually active teen couples use any method at all. Nonuse is also a serious problem among older women. Overall, 21% of US women who are at risk for unintended pregnancy are unprotected. If nonusers adopted currently available methods in the same pattern as their contraceptive-using peers, unintended pregnancies in the United States would decline by 57%.

High unintended pregnancy rates and high abortion rates are not inevitable. Other nations such as England, France, and the Netherlands do not share our problem despite similar patterns of sexual exposure among young people. These nations have managed to make effective education for young people and accessible services a reality. In the US, however, there are many obstacles to be overcome. Science may help, with more effective and more appealing contraceptive methods, but social, political, and economic dilemmas confound our efforts. It is a national disgrace that funding for family planning services is inadequate and that we do not have a forward-looking national policy and leadership. We have not even managed to use our most powerful educational tools such as television. These same dilemmas also impede contraceptive research and development and jeopardize future options for our children and grandchildren.

Increased federal support for research is needed. Worldwide, public and private funding for contraceptive research has declined in real dollars since its peak in 1972. Private sector research in this field has declined dramatically. Fifteen years ago, eight US pharmaceutical companies were involved in contraceptive research; today only one remains active. Nonprofit contraceptive research programs in this country estimate that an increase in their annual expenditures from the current level of $30 million to $53 million could be used productively and would make a significant difference in the pace of contraceptive development.

Economic, social, and political problems also have other less obvious but significant consequences. Decisions by manufacturers to withdraw the Saf-T-Coil, Lippes loop, Copper T and Copper 7 intrauterine devices were based on economic considerations, weighing profit and potential product liability; spermicide manufacturers, too, are confronting product liability issues.

Morning-after hormonal treatment is another interesting example. The treatment is simple: two tablets of Ovral—ethinyl estradiol, 50 μg, and norgestrel, 0.5 mg—taken within 12 to 72 hours after unprotected intercourse, followed by two additional tablets 12 hours later. The efficacy is excellent: a failure rate of less than 2% can be expected when this method is used after an isolated instance of unprotected intercourse. But despite the ready availability of the drug, morning-after treatment is rarely prescribed. It has no champion to market and distribute it. Potential profit for the manufacturer probably would not justify the cost of obtaining approval from the Food and Drug Administration (FDA) for a new indication for the drug. In addition, product liability and the possible social costs of marketing a postfertilization method are involved. So the manufacturer has never sought FDA approval, and the FDA has no other mechanism for approving drug indications. Without FDA approval, even family planning specialists who know about it have had difficulty making morning-after treatment available; policy makers for public clinics regard FDA sanction as an important safeguard. Meanwhile, condoms break, partners return unexpectedly, diaphragm equipment is forgotten in packing for a weekend trip, and women are raped. Effective postcoital contraception is needed. Education, accessible services, and a tiny expenditure for drugs are all that would be required. Although orphan-drug provisions may make FDA approval possible for a low-profit product, no good mechanism exists in this country to assure its availability, no matter how desirable.

The cervical cap, approved in 1988 by the FDA, will face similar problems as a low-profit product, and the economics of profit and product liability are likely to be as important as science in determining the destiny of future possibilities such as contraceptive vaccine.

Current options are also limited by political and social considerations. Long-acting injectable progestins, widely used in other countries, are not available in the United States, and, for want of a company with the political courage to distribute it, the once-a-month antiprogestin, RU486, already in use in France, is unlikely to become an option here. A vocal antiabortion minority extends its concerns to include

medical agents like RU486 that may affect postfertilization or implantation events. The current political power of this minority has stalemated federal policy and even medical research in this area for most of the past decade.

When it comes to the future of contraception, the crystal ball is murky. Science is still a steadfast hero, with monumental accomplishments and promising possibilities: spermicides and barriers that provide improved protection against both pregnancy and sexually transmitted infection; refined systemic steroid methods, possibly even for men; vaccines; and, in the more-distant future, a new generation of systemic methods that act on pregnancy-specific targets to block fertility without disrupting normal hormonal events. Bringing possibilities to actuality and making them available are the difficult problems. Coherent public policy and funding commitment are lacking; without them, better options will slip elusively farther and farther into the future.

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Hysterectomy and Ovarian Removal—A Major Health Issue in the Perimenopausal Years

In their early 40s, many women begin showing the first signs of approaching menopause—their periods get closer together as the follicular and luteal phases of the cycle contract, and fertility is lessened. Even though the cessation of periods does not occur until an average age of 51, physicians should begin much earlier to advise ways of making the transition into the postreproductive years as healthy as possible. The importance of exercise and a high-calcium, low-fat diet in preventing heart disease and osteoporosis are discussed elsewhere in this issue. Helping patients give up smoking, excessive alcohol use, and drug dependency are other ways to ease the menopausal transition.

Preserving the uterus and ovaries whenever possible is of paramount importance. Currently about a third of women in the United States have had a hysterectomy by the age of 60; their average age at the time of hysterectomy is 43 years. Many of these women have both ovaries removed as well; the National Center for Health Statistics reports that bilateral oophorectomy was done at 25% of hysterectomies in 1965 and at 41% in 1984.[1] The most common indications for hysterectomy since 1970 have been fibromyomas (27% of cases), prolapse (21%), and endometriosis (15%), with cancer being the indication in 10% of cases.

While some hysterectomies are necessary to save lives and relieve suffering, others are more elective. The prevalence of hysterectomy in the US—33% by age 60—contrasts substantially with a 13% prevalence rate in the United Kingdom and a 9% rate in France.[2] One reason to avoid hysterectomies whenever possible is the mortality rate (1/1,000), pain, and the expense of this major operation. In addition, several studies have shown an increased rate of cardiovascular disease in premenopausal women who have had a hysterectomy, even when one or both ovaries are preserved, indicating a possible hormonal function of the uterus. Sexologists are concerned that as many as a third of women having a hysterectomy, even with preservation of the ovaries, notice a diminution in intensity of excitement and orgasm, which is probably explained by the absence of cervical stimulation (which may enhance sexual excitement) and the diminution of pelvic engorgement after obliteration of the venous plexus in the broad ligaments. A Finnish gynecologist compared total to supracervical hysterectomies and found a better preservation of sexual response after the supracervical operation.[3] Preserving the cervix obviously leads to the risk of carcinoma of the cervix. This disease is easily detected by a Pap smear, however, and a woman may wish to continue having Pap smears if cervical stimulation is important to her.

There is currently a serious debate about removing healthy ovaries at the time of hysterectomy to prevent ovarian cancer. On the one hand, ovarian cancer occurs in about 1% of women and is a devastating disease. It has a low survival rate because it is difficult to detect in its early stages by pelvic examination. On the other hand, a woman undergoing bilateral oophorectomy suffers serious menopausal symptoms and an increased risk of heart disease unless she uses replacement estrogen. Even with replacement estrogen, she may suffer from a loss of libido, vigor, strength, and emotional well-being. Replacement of androgens may alleviate these symptoms,[4] but dosages and the safety of this approach need to be researched.

Reducing the number of elective hysterectomies should be made easier by new therapies for common gynecologic problems. Danazol, gonadotropin-releasing hormone, and conservative surgery are being used for endometriosis. Slowly growing fibromyomas can simply be watched over time and monitored with ultrasonography if desired. Myomectomy can be used for large symptomatic fibromyomas, and laser ablation or resection of the endometrium is available for the menorrhagia often seen with submucous fibroids. The trend toward lower parity will make symptomatic pelvic relaxation less common. A careful avoidance of unopposed estrogen replacement and the use of progestogens for endometrial hyperplasia will reduce the incidence of uterine cancer. These alternative methods of treatment should be evaluated before hysterectomy whenever possible to enhance the physical and psychological well-being of perimenopausal women. When oophorectomy is done, careful attention must be given to hormonal replacement. The effectiveness and route of androgen replacement should be a field of vigorous research.

Overall, women should be given full information about the cardiovascular, oncologic, and sexual implications of hysterectomy and prophylactic ovarian removal. They should decide their course in a more collaborative way than is the current practice.

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Health Promotion—Advice for Women

COUNSELING HEALTHY WOMEN on how to remain healthy includes reminding them to fasten their seat belts, update their immunizations, and limit their coffee, alcohol, and other drug consumption, as well as discussing smoking cessation and weight maintenance or reduction.

Smoking should be forcefully proscribed. Smoking as few as one to four cigarettes per day is associated with a twofold increased risk of fatal or nonfatal myocardial infarction in women. Women who smoke are at increased risk for cancer of the lung, larynx, bladder, pancreas, and perhaps both in situ and invasive carcinoma of the cervix. Smoking reduces fertility, increases the rate of spontaneous abortions, increases the incidence of placenta previa and abruptio, and retards fetal growth, resulting in infants with a lower average birth weight. Even more alarming are the data that suggest that there may be a long-term effect on children as a result of maternal smoking during pregnancy. The damage to children as a result of passive smoking is well documented, as is the increased incidence of skin wrinkles in their mothers.

Exercise should be liberally prescribed by physicians. Weight reduction programs that incorporate regular exercise improve a woman's chances of maintaining weight loss. Not only are calories expended but appetite is decreased, perhaps as a result of increased levels of endorphins. In addition, exercise increases the metabolic rate for several hours after the exercise period has concluded. Improved cardiovascular fitness, lowered blood pressure, and a better lipid profile also accrue to women who exercise regularly. Perhaps most important, there are psychological benefits, and women can be reminded that pursuing fitness can be fun.

Finally, to promote a woman's continued good health, clinicians are well advised to educate their women patients about safe sexual practices. As the incidence of some sexually transmitted diseases, including human immunodeficiency virus infections, rises, the need for open and frank discussion becomes more compelling.

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* * *

What if in my waking hours a sound should ring through the silent halls of hearing? What if a ray of light should flash through the darkened chambers of my soul? What would happen, I ask many and many a time. Would the bow-and-string tension of life snap? Would the heart, overweighted with sudden joy, stop beating for very excess of happiness?

HELEN KELLER

Women and Medicine

Surviving and Thriving

SUSAN D. WALL, MD, *Contributing Editor*

Juggling Motherhood and Medical Training

EDITOR'S NOTE: Keteri Fleet is a second-year resident in internal medicine at Highland General Hospital, Oakland, CA. She is married to a tugboat engineer and has recently had her first child.

AS A JUNIOR INTERNAL MEDICINE RESIDENT in the busy county hospital and trauma center of Oakland, California, I am in the fortunate but frequently demanding position of being a new mother and continuing my internal medicine training. Many women physicians like me aspire to both these traditionally full-time jobs, confident in the belief that personal fulfillment will be richer and career commitment more grounded and balanced. My age—37—has a lot to do with why I selected the present time to begin my family. In my own life, I see a number of factors that have contributed to making this dual career possible.

I am lucky to occupy a part-time position as an internal medicine resident, which stretches my training over three instead of two years. Working 7 to 8 months out of 12 gives me the flexibility I need to focus on family commitments. The biggest drawback to this schedule is some loss of continuity in my training—a loss that I accept as a consequence of my personal choices. I recently have been granted an extended leave of absence by my medical director. I view this as a very special privilege that is not granted to many residents in my situation.

I practice medicine in an era when the traditional time and energy demands on house staff are being reevaluated. Many training programs are beginning to recognize the damage done to patient care and physician health and well-being by 36-hour shifts and 120-hour workweeks. My training program is in the process of reassessing call and back-up schedules with the goal of shaping a more humane training experience. I am committed to this effort because it protects both patients and staff, although I recognize only too clearly the economic and bueaucratic obstacles that need to be overcome. I predict that as new scheduling arrangements emerge, more women and men physicians will feel freer to participate more fully in family life.

A strong support system of family and friends is essential. Even with the most humane career schedule, a mother or future mother may feel torn between the desire to excel medically and the desire to care for her child. I am fortunate to have a flexible spouse and a close network of family and friends who have already given me immeasurable moral and practical support. After the recent birth of my son, friends and family helped by doing my shopping and cooking and delivering entire meals; several friends took turns staying overnight to help because this was my first child and my husband was away.

Of particular importance to me in aspiring to these two vocations was learning to accept my limitations and knowing when to say no. The image of Superwoman is seductive, and I like to believe I can do it all, with ease. I find repeatedly, however, that when I admit I am over my head and need to stop and regroup, I am able to accomplish all the more. I am learning to accept the help of others with some humility.

Finally, there is health—the bottom line. Luck plays a part, but protecting my physical, mental, and spiritual health also requires vigilance. No one else can do it for me, and in many ways it should be my highest priority. It requires time, which on occasion may involve sacrificing both family and career. I eat a sensible diet and watch my food intake carefully—lots of vegetables and fruit, enough protein, limit coffee to one cup a day, avoid junk foods—and I take vitamins regularly. I try to swim or run for an average of three to four hours a week. I also try to take another three to four hours a week to be alone. After exceptionally long hours at work, I make sure I get enough rest.

This all sounds so straightforward and pat, and, yet, the living of it can be incredibly frustrating. Judgment and the ability to set priorities are coming to me with time—something there is precious little of. So far, so good, with the help of friends and loved ones.

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Buying Time for the Good Things in Life

EDITOR'S NOTE: Linda M. Dairiki Shortliffe, MD, is an Associate Professor of Surgery (Urology) at Stanford University. She sees patients, teaches students and house officers, and was the principal investigator of a four-year extramural grant to investigate the immune aspects of prostatitis. She is a member of numerous university committees. She is married to an internist, and they have two daughters, aged 6 years and 9 months, respectively.

FOR MOST PHYSICIANS the primary obstacle in achieving professional and personal goals is insufficient time. For many women physicians, this lack of time is important in coping not only with their professional work but also with their personal lives and their often traditional views of child-rearing and care, household organization, and marriage. Because many physicians are high achievers, perfectionists, and conscientious by self-selection, this lack of time makes doing their professional and personal work in a satisfactory, if not excellent, manner difficult and sometimes impossible. My life is not perfect and will never be, but recognizing this has caused me to change priorities and to adapt to different circumstances in order to achieve a "balance" between my

professional and personal life. This balance is, however, constantly changing.

I have become an expert at delayed gratification. With medical and surgical training being what it is, I am used to the planning and the loss of freedom that such a life entails. My husband and I have found that last-minute or inadequate planning in both our professional and personal lives adds to frustration and chaos. We were married 11 years before we even completed our medical training. For my husband, this was medical school, a PhD in medical information sciences, and an internal medicine residency; for me it was medical school and a urology residency. Although we both love animals, we waited nine years after we were married—until my husband finished his residency—to get a dog because we wanted one of us to be home most evenings to play with and care for the dog. We also waited 12 years after we were married before we had our first child. At that time, we thought our schedules could finally have some flexibility and that we could afford the kind of child care that we needed. It was five years after that, when our daughter developed some independence, before we felt that we could handle a second child.

As our lives have changed, so have our needs: we need a lot of help and need to pay for it. In essence we have had to buy back our free time. This has been a difficult realization because we had always done and expected to do many of the chores that we now pay others to do. We also accept that we can do some of these chores better than those we now pay to do them, but we have them done, nevertheless. When we were residents, we recognized that we needed help with housekeeping when neither of us wanted to spend our precious hours off scrubbing toilets and bathtubs. With the birth of our children came the inevitable question of child care. Although we knew from the beginning that our irregular work hours required live-in help, our perceptions of what this person should be and do have changed with experience. After the birth of our first daughter we had a delightful au pair who cared for our child during the day. Although this was a tremendous help, we found that rushing home to cook every evening, with grocery shopping, house cleaning, laundry, and errand running on the weekends, were robbing us of time with our daughter. After nine months we decided that we needed a reliable, careful, mature nanny and housekeeper for all of us, and that we would be willing to pay top wages and benefits to such a person. This has given us time to spend with our children and to do things other than daily chores. In addition, a live-in nanny allows support when one of us is traveling, attending an evening meeting, or called in for medical emergencies. Selecting someone to live with us has also provided us the benefit of getting to know better the personality and values of the person who cares for our children. In the past few years we have added the help of regular housecleaners and gardeners.

We have also "bought" time for ourselves by minimizing errands and household trips. We try to buy several months of clothes at once. Often we buy our Christmas gifts in the summer while on vacation just to prevent the hectic seasonal shopping. We try to plan our shopping so that we do not have to make extra trips to prepare special dinners or find last-minute gifts.

I continue to try to learn new ways of preserving my time for the things that I want to do rather than the things I need to do. This has meant not only setting priorities and goals but also adjusting them because they are often unmet. Unfortunately, this usually means "robbing Peter to pay Paul" because things are not perfect.

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Managing the Yin and the Yang

EDITOR'S NOTE: Nadine Bruce, MD, is an Assistant Professor of Medicine and Deputy Program Director, Integrated Medical Residency Program, at the University of Hawaii. She redirected her career from private practice to academic medicine ten years ago. She is married to Hans-Jürgen Krock, PhD, who is an Associate Professor and Director of the Oceanographic Research Laboratory at the University of Hawaii.

I HAVE BEEN ASKED to share some key elements that have allowed me success in balancing my professional and personal lives. My success is a delusion, but because I do not know this, I function fairly well.

The chaos of daily life would rapidly impair me if I did not take time to smell the flowers. Using one's senses to appreciate the beauty and wonder of the world takes no additional time, whether it is the sight of an infant's smile or the feel of a hot shower at the end of a long day. I am a classical music and laughter junkie, and I must have daily doses of both.

Personal time is essential and should be scheduled as rigorously as patient appointments. I block out mini-breaks on my daily work schedule for a quick lunch with a friend or a detour to the bookstore on the way to an evening meeting. The most treasured possession in my office is my couch, inherited from the department chair. I have learned to take catnaps without guilt. Putting my feet up and taking my shoes off make the paperwork go faster and more pleasantly. I set aside half a day a week to do something fun for me. An evening a week and weekend breakfasts out are reserved for "dates" with my spouse. Holidays are sacred, and they are used for leisure activities only. Long weekends to the outer islands, sometimes combined with a short continuing medical education course, are taken at least twice a year. Annual vacations—the more exotic, the better—ensure my survival the rest of the year. When I am experiencing mountain sickness in Tibet, it is easy to forget the petty criticisms of my detractors at work, the departmental project six months overdue, or the fact that my bedroom roof continues to leak despite multiple repairs.

Knowing people care about me has gotten me through many rough times both professionally and personally. My spouse is my helpmate in every sense of the word. I could not afford the time or energy required to maintain a relationship if I had just a mate or, worse yet, a hindermate. I have sought out male mentors since the inception of my career. They have helped pave a smoother way for me in this male-dominated profession. I have one intimate friend and one familiar (my cat) to share my joys and sorrows. I actively maintain relationships with family and friends; they are too precious to take for granted. I avoid the mean-spirited.

I have learned to create time. Ten years ago I took a speed-reading course. This skill quarters the time I spend on administrative duties, enhances my studying, and allows me to indulge in pleasure reading to a degree I never considered possible. Weekly and daily "to do" lists both at work and at

home guarantee my completing tasks on a timely basis. Finding ways to do two things at once is a game I play: riding the exercise bike while watching the news on television, reading a paperback novel while waiting in the bank line, restaurant breakfast meetings for business or pleasure. Years ago I discovered mail-order shopping.

It took no time at all to relegate housework to where it belongs on my priority list—off the list. I have made the bed twice in the past decade. Ironing is a word not in my vocabulary. I once made a promise to my spouse that I would cook for him, and I do this faithfully—every Sunday evening. My intense need for privacy keeps me from hiring household help, so I clean the house myself, as infrequently as possible. I have accumulated an arsenal of space-age cleaning tools. Not only am I a speed-reader, I am also a speed-cleaner. My spouse and I divide the absolutely necessary household duties according to who detests doing what less. He does the laundry, vacuums, changes the unmade bed, and attempts household repairs. I feed the cat, water the houseplants, empty the wastebaskets, take out the garbage, wash the dishes every Sunday evening, and mow the lawn. (Actually, I only mow the front lawn, primarily to appease the neighbors; the backyard, spared from the neighborhood view, is our minijungle.) Grocery shopping is done together, our Sunday social event.

Ten years ago I redirected my career because private practice was making me dull. I actually work more hours in academic medicine, but I have more control of those hours. Instead of being on call 24 hours a day every day, I now take call only one week out of seven. I am running my career instead of having it run me.

I rejected the Superwoman Syndrome as soon as I learned of its existence. I never wanted to be Superwoman. It is hard enough just being. My goal is to become Ordinary Woman, at which point my life will function ideally. I do not have to have it all. I do not even want it all. I have learned to say no. I have graciously accepted my deficiencies and failures. I actively strive to become downwardly mobile, and I very much enjoy my "dinky" (double income, no kids) status.

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The Successful Mix

EDITOR'S NOTE: Peggy Fritzsche, MD, is a Professor of Radiology at Loma Linda (California) University Medical Center. She is active in local and national medical organizations and is past president of the medical staff at her hospital. She is married to Anton N. Hasso, MD, a neuroradiologist; they have two grown sons.

THERE ARE SEVERAL FACTORS that have allowed me to successfully mix my personal and professional lives. I have benefited by the inspiration of my mother, who urged excellence in schoolwork and household tasks. She encouraged her children to excel: "No one can ever take education and achievements away from you." This early influence directed many of my decisions, even during childhood, and I learned to eliminate activities that were not goal-oriented. Self-discipline and productivity were expected, and they followed naturally.

The inspiration of my teachers and professors encouraged me to pursue a medical career. This was especially important when peers suggested less demanding alternatives. The inspiration of my spouse has always supported my efforts to teach locally and nationally, learn new skills, write, and participate in administrative and committee work. His response to my professional invitations is always the same: "You accepted, didn't you?"

Being a skilled observer of other people, procedures, events, and conversation offers a distinct advantage. There also is value in seeking new information. I gather the facts and incorporate with dedicated discipline anything of importance that will improve my personal life or professional activities. The new ideas may relate to improved lecture presentations, procedure techniques, writing skills or proficiency, or committee work. I evaluate committee commitments and identify the needs of the group. I then volunteer according to my talents or interest in learning new information. I make it customary never to turn down an opportunity to serve, meet new people, or experience new things, even when it is inconvenient to previous plans or my personal life.

There is a positive aspect to every event, so I do not waste time on regrets—that is only negative reinforcement. I practice reliving the vibrant and exciting times, and I smile for myself.

Personal improvement also is enhanced through changing behavior relating to health, exercise, and nutrition. Discipline and mental strength are helpful traits. Flexibility is necessary to meet new challenges, and it may require conscious compromise in the area of mundane household tasks. I make my time and efforts meaningful based on what activity will have importance five or ten years in the future.

The mind must be in touch with the body daily. If there is a deficiency in sleep, fresh air, movement, or diet, then I make adjustments to my schedule as soon as possible. It is important to pace myself and avoid stress. I use relaxation techniques that can be practiced anywhere: office, car, plane, amphitheater. Many times events must be rescheduled or cancelled in order to observe mind and body alignment. My body needs daily aerobic exercise, and I frequently use vacation time for physical activity.

I am a pilot, and I love to practice loops, rolls, and spins on the weekend in my Bellanca Super Decathlon aerobatic airplane.

Close monitoring of my activities by my spouse and me prevents overload. Our regular sharing of activities and discussions helps to identify priorities. The advantage of two viewpoints on one topic provides an additional valuable perspective. My understanding helpmate participates in managing the children and household—the secret to my happiness and success.

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The Juggled Life

EDITOR'S NOTE: Leona M. Bayer, MD, practiced medicine in the San Francisco area for 50 years. She was also on the clinical staff of Stanford University School of Medicine. On the occasion of her 85th birthday, she was honored by the Women's International League for Peace and Freedom and on two previous occasions by the Physicians for Social Responsibility.

DICTIONARIES DEFINE JUGGLING IN MANY WAYS, most of them implying trickery or deceit. Perhaps those of us who try to

juggle our personal and professional lives are deluding ourselves. In any case, if, as professionals, we choose or drift into a complex life-style, it is essential that each element of the game be satisfying. The choice of medicine as a career is a good start because it offers so many subspecialties, so much flexibility.

When I entered Stanford University, I planned to study chemistry and received my bachelor of arts degree with that subject as my major. A summer job in the laboratory of a brilliant clinician, Thomas Addis, inspired me to combine scientific work with the care of people. In the fall of 1923, I enrolled in Stanford Medical School.

In our class of 60, five of us were women. We were easily accepted. Tension in the class came not from our presence but from the plan to cut the class size to 50 during the freshman year; this unfortunate policy later was changed. In the 1920s, women were the beneficiaries of the successful suffrage movement. Because we were too young to have participated in the movement, we hardly realized how widely it had opened doors for us.

I was fortunate to have many meaningful interests in common with my husband, Ernst Wolff, a pediatrician. Because we shared medical offices, I was free to work part-time as a clinician, taking time out to be with our children and even to participate in academic research and writing. Our involvement with the issues of peace and justice grew out of the Depression years, the Spanish Civil War with its culmination in World War II, and the bitter McCarthy era. Ernst's service in World War I gave added force to his commitment.

Our most sustained protest was a vigil against the Vietnam War, organized locally by the San Francisco branch of the Women's International League for Peace and Freedom, an organization in which I have long been active. The vigil began in Union Square on Veterans' Day, 1966, and continued every Saturday until the war ended in 1975. I was there most weeks and Ernst often joined the women and a few other participating men. Public reaction ranged from warm support through indifference, hostility, and calumny.

My immediate medical community has been tolerant of but largely indifferent to my global concerns. Among the local women physicians of my generation, only two or three participated in similar activities. This surprised me. I had expected that women enterprising enough to go into medicine in the 1920s and 1930s would be moved to join the wider struggle for liberation and peace. Perhaps the "younger generation" is different in this regard. Maybe they are more ready to struggle for a gentler world. Or maybe they are more realistic in acknowledging how little, how slowly, progress can be achieved. Certainly, the rewards of medical efforts are more tangible: the right diagnosis, the happy cure, the rare discovery, the published paper. These are results that give and bring real satisfaction. Nevertheless, I have found that my simple persistence over the years in community affairs and activist organizations is appreciated by successive generations of co-workers, perhaps as a sign of a reassuring continuity in the ever-changing search for a better life.

LEONA M. BAYER, MD
San Francisco

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Super Paper Doll
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Women and Medicine

Women Physicians and Organized Medicine

LOUISE L. McDONALD, MD, *Foster City, California*

"Like most women, you won't practice. You're taking the place of a male student who *would* go out and practice medicine, but otherwise you have the qualifications so I can't reject your application." With these words from an assistant dean, I was admitted to medical school in 1962, one of five women in a class of 120. Currently about 16% of this country's physicians are women, and female students make up more than a third of today's medical school classes.

Times have changed for women in medicine, but in some ways they have not changed enough. For instance, although the number of practicing female physicians rises every year, the proportion joining organized medicine does not increase accordingly. It is difficult to convince women to join and more difficult to get them to participate. Thus, women physicians remain underrepresented in organized medicine despite their growing numbers. Why? After all, organized medicine speaks for *all* physicians, gender notwithstanding. It gives us all the opportunity to have some influence over factors that affect our practices. And, for female physicians, membership and participation in organized medicine helps overcome whatever prejudices may remain against women in medicine. So why don't more women join?

To answer this question and to solve the problem, the Council of the California Medical Association formed a committee on women in medicine in 1986. The committee is composed of about a dozen women physicians selected from various parts of the state and from different age groups, specialties, and practice styles. They represent their female colleagues and explore means by which organized medicine can better meet the needs of women physicians. The committee has adopted the following goals:

- To define and examine issues that are important or unique to women physicians;
- To make recommendations about the ways organized medicine can serve women physicians;
- To develop avenues that encourage the greater involvement of women physicians in organized medicine.

To achieve these goals, we began by conducting a survey of 1,300 California female physicians—500 who were members of their state medical association and 800 nonmembers. The response rates were 64% and 31%, respectively. The information obtained from the survey failed to reveal why more women do not join organized medicine. Demographic characteristics that our committee members thought might be important, such as marital status or number of children at home, were consistent between members and nonmembers. And the majority of both groups of female physicians looked upon the state medical association as an "old-boys club." The survey did, however, give us a better understanding of how women physicians view organized medicine and of what they want organized medicine to do for them.

Based on the survey responses, the Committee on Women in Medicine is developing a program to recruit female physicians into the California Medical Association and to meet their needs. Because statewide recruitment is usually less successful than peer-to-peer contact at the county medical society level, our committee is encouraging county medical societies to form their own committees on women in medicine with whom we can coordinate activities. At the present time our committee members are beginning to recruit female physicians in their own counties who are not members of the state association by writing letters co-signed by the county medical society president. Follow-up mailings and telephone calls are also planned.

With assistance from the Committee of Medical Student Representatives, our committee has organized a mentor pilot program at the Loma Linda (California) School of Medicine. Women physicians practicing in the community are being asked to serve as mentors to women students at the medical school. These mentors will advise the students about medical practice, provide them with information about organized medicine, and discuss various problems shared by women physicians. If the mentor program succeeds at Loma Linda, similar programs will be established at the other medical schools in California.

To address concerns particular to women physicians, the committee plans and presents workshops in both the northern and southern parts of our state. Most of the members and nonmembers surveyed favored this idea. They want to hear about solutions to career and family conflicts, leadership training, and practice management. The committee also solicits authors for articles about women's issues for publication in the medical association's socioeconomic journal, *California Physician.*

We committee members think that it is important for us to remain visible to the rest of the organization by taking a stand on matters that affect women generally. Thus, each year we introduce resolutions before the House of Delegates of the California Medical Association. In 1988 the house adopted our resolution urging medical training facilities to establish on-site child-care centers for the benefit of medical trainees.

(McDonald LL: Women physicians and organized medicine, *In* Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:777-778)

From the Foster City Pediatric Medical Group, Foster City, California. Dr McDonald is Chair of the California Medical Association Committee on Women in Medicine.

Reprint requests to Louise L. McDonald, MD, Foster City Pediatric Medical Group, 1295 E Hillsdale Blvd, Foster City, CA 94404.

The California delegation introduced the resolution to the 1988 American Medical Association House of Delegates, who also referred the resolution for action.

Our Committee on Women in Medicine has initiated a liaison with the California State Bar Committee on Women in the Law. Many interests and concerns are common to women in all professions, and an exchange of ideas can be enlightening and useful.

Through the activities of the Committee on Women in Medicine, we want to communicate the message that organized medicine is for *all* physicians. As their number increases, women physicians cannot remain in the background, letting others set the policies for them. They must participate in the decision-making process. When enough of them do so, a committee like ours may no longer be needed; that is our ultimate goal.

* * *

A blank wall of social and professional antagonism faces the woman physician that forms a situation of painful loneliness, leaving her without support, respect, or counsel.

Elizabeth Blackwell (182? to 1910)

Women in Academic Medicine

Equalizing the Opportunities

DORIS G. BARTUSKA, MD, *Philadelphia*

What inspires women physicians to select a career in academic medicine and assume leadership roles in research, teaching, administration, and a clinical specialty medical practice?[1] Academia provides a supportive and creative environment wherein ideas can be shared, research to solve medical problems conducted, and clinical medicine practiced while the art and science of medicine are taught to the physicians of tomorrow.

The work is hard. The average academic physician spends 63 hours per week in professional activities—about 20 hours in research, 12 in teaching, 16 in patient care, 12 in administration, and 3 in other, related activities. The hours will vary for those concentrating more on patient care than on research.

All faculty members have substantial administrative and committee responsibilities, as well as such extra duties as editing medical journals, serving on peer review panels, continuing their education, and obtaining research funding. Teaching is a stimulating and exciting aspect of academic medicine. One must love it.

Where do women stand in academic medicine? Almost 19% of medical school faculty members are women, but 67% of those are in the entry-level ranks of assistant professor, research instructor, or clinical instructor (Table 1). In 1985, 5% of professors were women; in 1987, 9.4% were women.[2] In 1988, there are two women medical school deans.

A review of career achievements has shown that full professors and most associate professors were in the upper third of their class rank academically in the four years of medical school.[3] Most of the assistant professors were in the middle ranks of their class. Career success, measured by academic rank in one study, is positively and significantly associated with academic standing at the end of the fourth year of medical school. In this group of assistant professors, most of the women physicians were married and had families of comparable size to those women in clinical or administrative medicine. Marriage and family responsibilities of this small group of women physicians did not impede their attaining professor rank. Career achievement was influenced more by motivation and personality and less by marriage status and family.

TABLE 1.—*Distribution of Medical School Faculty in the United States by Sex and Rank, 1987**

	Male		Female	
Rank	*Number*	*Percent*	*Number*	*Percent*
Professor	14,694	31.5	1,023	9.4
Associate Professor	12,133	26.0	2,087	19.3
Assistant Professor	15,611	33.4	5,297	48.9
Instructor	3,268	7.0	1,966	18.1
Other	945	2.0	457	4.2
Missing	27	0.1	10	0.1
Total	46,678	100.0	10,840	100.0

*From Women in Medicine Data Source.[2]

A recent study of promotions at Johns Hopkins University School of Medicine (Baltimore) showed that there were no significant differences between promotions for clinical and research faculty members.[4] The responses to a questionnaire indicated, however, that faculty members perceived clinician-teachers as less likely than basic science researchers to be promoted. Those who were promoted had twice as many articles published in peer-reviewed journals as those who were not promoted.

The American Medical Women's Association has a leadership training program for medical students and physicians, the goal of which is to enable women to attain positions of leadership in academia and medical societies and to influence policies that relate to women's health and child and dependent care.

We must encourage our talented women physicians by recognition, support, and financial assistance to enter and succeed in academic careers. More academic women physicians should be in leadership roles—delivering scientific papers and chairing sessions at medical meetings, having important positions in specialty societies, being politically active, chairing departments, being deans, and having a role in organized medicine to influence health care policy. Certainly, department chairs must monitor career paths and discuss the criteria for promotion in academic medicine with junior faculty members.

Everyone needs a mentor—preferably as early in medical training as possible—who will serve as a resource in career advancement, graduate opportunities, and credential sup-

(Bartuska DG: Women in academic medicine—Equalizing the opportunities, In Women and Medicine [Special Issue]. West J Med 1988 Dec; 149:779-780)

From the Division of Endocrinology and Metabolism, Department of Medicine, Medical College of Pennsylvania, Philadelphia.

Reprint requests to Doris G. Bartuska, MD, Division of Endocrinology and Metabolism, Medical College of Pennsylvania, 3300 Henry Ave, Philadelphia, PA 19129.

port. Women students may find inspiration and role models more easily now that women physicians are assuming leadership positions on medical school faculties. Medical students considering academic medicine should discuss their interests with the department chair as soon as they can.

We are, finally, starting to equalize the opportunities for women in academic medicine.

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AGNES HOCKADAY, MD

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CONTINUING MEDICAL EDUCATION

(Continued from Page 676)

January 29-February 3—**Clinical Update in Anesthesiology.** Tucson Hospitals Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray G. Atnikov, MD, c/o Box F110-63, Blaine, WA 98230. (604) 874-5291.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sat-Sun. Contact: Murray G. Atnikov, MD. (604) 874-5291.

February 27-March 2—**17th Obstetric Anesthesia Conference.** Dept of Anesthesiology Ohio State at Sheraton Waikiki Hotel, Hawaii. Mon-Thurs. Contact: Arlene Rogers, Ohio State University Hospitals, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 16-19—**Obstetrical Anesthesia: 1989.** UCSF at Hotel Meridien, San Francisco. Thurs-Sun. Contact: Anita Edgecombe, UCSF, C 450, Box 0648, San Francisco 94143-0648. (415) 476-2273.

March 18-19—**34th Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: LACSA, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581, ext 320.

June 15-18—**California Society of Anesthesiologists: 1989 Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $150. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

January 19-21—**Cardiology 89: New Pharmacology, New Procedures, New Pacemakers.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott Hotel. Thurs-Sat. 16 hrs. $300. Contact: Nancy Donegan, Deverman & Associates, 7777 Alvarado Rd, Ste 280, La Mesa 92041. (619) 668-9091.

February 15—**29th Annual Cardiology Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Building, Chico. Wed. Contact: Bonnie Wells, Enloe Hospital. (916) 891-7375.

February 24-25—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Grand Hotel, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 9-11—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at Maui, Hawaii. Thurs-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

March 10-11—**Risk Factors for Cardiovascular Disease: Lipids, Diabetes and Hypertension.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. $200. Contact: UCSF.

March 16-18—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Westin Maui Hotel. Thurs-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 31-April 1—**Coronary Heart Disease Update.** Medical Education Resources at Caesar's Palace, Las Vegas. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 14-15—**Update in Clinical Cardiology for the Primary Care Physician.** Medical Education Collaborative at Las Vegas, Nevada. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

May 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Fisherman's Wharf. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 16-17—**Coronary Heart Disease.** Medical Education Resources at Hyatt Lake Tahoe. Fri-Sat. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

July 7-8—**Case Studies in ECG Interpretation and Arrhythmia Management.** Medical Education Collaborative at San Diego. Fri-Sat. 12 hrs. $295. Contact: MEC, 133 S Van Gordon St, Ste 315, Lakewood, CO 80228. (800) 442-6632.

EMERGENCY MEDICINE

January 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. $450. Contact: UCSD.

January 26-30—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Maui Marriott, Maui, Hawaii. Thurs-Mon. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

January 27-29—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

February 19-24—**Emergency Medicine.** UCD. Sun-Fri. Contact: UCD.

April 5-7—**Advances in Emergency Medicine.** UCSF at Stanford Court, San Francisco. Wed-Fri. $380. Contact: UCSF.

March 2-5—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Sheraton Universal, Los Angeles. Thurs-Sun. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

March 20-24—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. $450. Contact: UCSD.

May 1-5—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

December 30-January 8—**Medical Acupuncture for Physicians: Part II.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. 10 days. 200 hrs. $3,200. Contact: UCLA.

January 6-7—**6th Annual Reider Laser Symposium—Urology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 19-20—**Third Urological Symposium.** Kenneth Norris Jr Comprehensive Cancer Center at Moseley-Salvatori Conference Center, Los Angeles. Thurs-Fri. 12 hrs. Contact: Louise B. Ball, Executive Secretary, PO Box J, South Pasadena 91030. (213) 680-2387.

January 21—**Innovations in Ankle Arthroscopy.** Mount Zion Hospital and Medical Center at Hyatt Union Square, San Francisco. Sat. 7.25 hrs. $275. Contact: Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

January 23-26—**Neurology Update.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Mon-Thurs. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 25-27—**12th Annual: Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wed-Fri. 21 hrs. $400. Contact: Edith S. Bookstein, NNN, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 8-10—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort, San Diego. Wed-Fri. 21 hrs. Contact: Bonny Mower, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 15-17—**22nd Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15.5 hrs. $345. Contact: UCSF.

February 17-18—**Advances in Skin Cancer Management: A Multi-Specialty Approach.** UCSF at Ramada Renaissance Hotel, San Francisco. Fri-Sat. 10 hrs. $250. Contact: UCSF.

February 20-22—**Clinical Hematology and Oncology: 1989.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, Conference Coordinator. (619) 457-8556.

(Continued on Page 784)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 782)

March 8-9—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn Union Square. Wed-Thurs. 14 hrs. $250. Contact: UCSF.

March 17-19—**Gastroenterology Update Cruise.** Center for Health Education at Queen Mary Hotel, Long Beach. Fri-Sun. Contact: Center for Health Education, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

March 17-23—**Internal Medicine 1989: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Fri-Thurs. 54 hrs. $495. Contact: Jacqueline Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 21-24—**Topics in Rheumatology II.** Straub Foundation at Ilikai Hotel, Honolulu, Hawaii. Tues-Fri. 16 hrs. $350. Contact: Juliana J. Woo, MPH, Straub Foundation, 846 S Hotel St, #302, Honolulu, HI 96813. (808) 524-6755.

June 12-16—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 26-30—**Advances in Internal Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

OB/GYN

January 6-7—**6th Annual Reider Laser Symposium—Gynecology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 16-20—**21st Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 38 hrs. $595. Contact: USC.

January 9-11—**Urogynecology.** American College of Obstetricians and Gynecologists at Kauai, Hawaii. Mon-Wed. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

January 12-14—**Obstetric Controversies.** American College of Obstetricians and Gynecologists at Kauai, Hawaii. Thurs-Sat. 16 hrs. $515. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

January 29-February 2—**Ob/Gyn.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

June 22-24—**Basic and Advanced Colposcopy.** American College of Obstetricians and Gynecologists at San Francisco. Thurs-Sat. 16 hrs. $600. Contact: ACOG Registrar, 409 12th St, SW, Washington, DC 20024-2180. (202) 863-2541.

OPHTHALMOLOGY

February 5-9—**8th Annual Squaw Valley Retinal Symposium.** Retina Faculty of UCD at Granibakken Resort, Tahoe City. Sun-Thurs. 16 hrs. $360. Contact: James W. Wells, Jr, MD, 3939 J St, Ste 210, Sacramento 95819. (916) 454-4861.

April 1—**Visions in Ophthalmology '89.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Sat. 5 hrs. $100. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

ORTHOPEDICS

January 21-28—**Orthopaedic Emergencies.** Scripps Memorial Hospital Encinitas at Kona Surf Resort, Kona, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 12—**1989 Interim Meeting of American Orthopaedic Society of Sports Medicine.** American Orthopaedics Society for Sports Medicine at Las Vegas, Nevada. Sun. Contact: AOSSM, 70 W Hubbard St, Ste 202, Chicago, IL 60610. (312) 644-2623.

PEDIATRICS

November 30—**Challenges in Perinatology: Are We Ready for the Future?** Perinatal Advisory Council of Los Angeles Communities at Sheraton-Universal Hotel, Universal City. Wed. 6 hrs. Contact: Marianne Gray, Executive Secretary. (213) 380-1790.

December 3—**Recent Advances in the Care of Children.** UCD at Hyatt Regency, Sacramento. Sat. 8 hrs. $125. Contact: UCD.

December 3—**7th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Educational Center, San Diego. Sat. 7 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 21—**Pediatric Cardiology for the Primary Care Physician.** Children's Hospital at Merritt Peralta Health Education Center, Oakland. Fri-Sat. 6 hrs. $75. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

January 27-29—**27th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott. Fri-Sun. 15 hrs. $225. Contact: Katherine Barky, MD, Childrens Hospital, PO Box 54700, Los Angeles 90054.

February 10-12—**Current Concepts in Pediatric Medicine.** Children's Hospital & Health Center at Marriott Hotel, San Diego. Wed-Fri. 18 hrs. $220. Contact: Children's Hospital & Health Center, Continuing Medical Education Office, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 20-22—**Pediatrics Update: 1989.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 24-25—**California Conference on Health Care for Foster Children.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 14 hrs. $125. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

March 9-11—**Brain Insults in Infants and Children: Diagnosis and Modern Management.** UCSD at Holiday Inn at the Embarcadero, San Diego. Thurs-Sat. 15 hrs. $325. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

March 17-18—**Hematology and AIDS: Neonatal & Pediatric Perspectives II.** Children's Hospital at Berkeley Marina Marriott Hotel. Fri-Sat. 12 hrs. $160. Contact: Kim I. Leadon, CME, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

March 30-April 1—**Pediatric Trends.** American Academy of Pediatrics at Waiohai Hotel, Kauai, Hawaii. Thurs-Sat. 16 hrs. Contact: CME Registration, Department of Education, AAP, PO Box 927, Elk Grove Village, IL 60009-5005. (800) 433-9016.

PSYCHIATRY

November 18-20—**34th Annual Group Therapy Symposium.** UCSF. Fri-Sun. Contact: UCSF.

January 22-27—**15th Annual Midwinter Program for Psychiatrists: Special Focus on Panic and Anxiety.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $385. Contact: UCD.

January 27-29—**New Advances in Cognitive Therapy.** UCSD at San Diego Marriott Hotel and Marina. Fri-Sun. 16 hrs. $375. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

RADIOLOGY

January 13-15—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: R. Dawne Ryals, PO Box 920113, Norcross 30092-0113. (404) 641-9773.

January 19-21—**Duplex Imaging.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sat. 16 hrs. $375. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

January 21-22—**Workshop on Percutaneous Disectomy.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Sat-Sun. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

January 23-25—**Neuroradiology Update 1989.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Mon-Thurs. 18 hrs. $375. Contact: Dawne Ryals, Ryals & Associates, (404) 641-9773.

January 23-27—**Combined Course—Neuroradiology Update and Magnetic Resonance Imaging.** UCSD at San Diego Marriott Hotel and Marina, San Diego. Mon-Fri. 21 hrs. $450. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 785)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 784)

January 24-27—**MRI for Technologists—Symposium and Workshops.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Tues-Fri. 21 hrs. $425. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

January 27-29—**41st Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 21 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

January 31-February 4—**15th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Westin Kauai, Hawaii. Tues-Sat. 20 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 23-25—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Rancho Mirage. Thurs-Sat. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

February 24-26—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel Rancho Mirage, Palm Springs. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, Ryals & Associates, (404) 641-9773.

March 5-9—**Thoracic Imaging '89.** Society of Thoracic Radiology at Hotel Del Coronado, San Diego. Sun-Thurs. 32 hrs. $400. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

March 10-12—**Musculoskeletal Imaging: The State of the Art.** Hoag Memorial Hospital at Four Seasons Hotel, Newport Beach. Fri-Sun. 16 hrs. $375. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

April 16-21—**9th Annual San Diego Residents Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sun-Fri. 39 hrs. $425. Contact: Dawne Ryals, Ryals & Associates. (404) 641-9773.

April 28-30—**14th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20 hrs. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

May 2-6—**9th Annual Mid-Pacific Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Royal Waikoloan Hotel, The Big Island of Hawaii. Tues-Sat. 19 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078

SURGERY

January-July—**Temporal Bone Surgical Dissection Courses: 1989.** House Ear Institute, 5 days per month. 53 hrs. $975. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 13-14—**11th Annual Postgraduate Course: What's New in General Surgery.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

January 27-29—**Annual Scientific Meeting of the Southern California Chapter American College of Surgeons.** American College of Surgeons at Palm Springs Riviera Hotel. Fri-Sun. Contact: SCACS, PO Box 3465, Los Angeles 90051-1465. (213) 483-1581.

March 9-11—**Knee Reconstruction Surgery: ACL Repair, Patella Alignment and Total Knee Replacement.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Thurs-Sat. 30 hrs. Contact: Bonny Mower, Conference Coordinator, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 15-17—**Perioperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. 16 hrs. $350. Contact: UCSF.

(Continued on Page 790)

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Consult the package literature for prescribing information.

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Contraindication: Known allergy to cephalosporins
Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.
Administer cautiously to allergic patients.
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea) 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever). 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology
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- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
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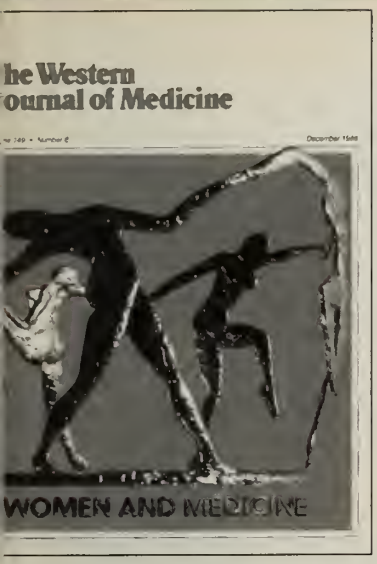


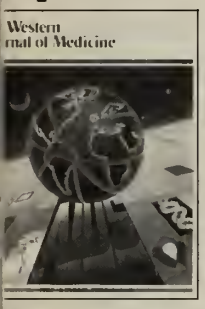
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients.

Some of the topics covered include liver disease in women, women and AIDS, women and heart disease, hysterectomy, PMS, ovarian cancer, women physicians and organized medicine, and career choices of women physicians.

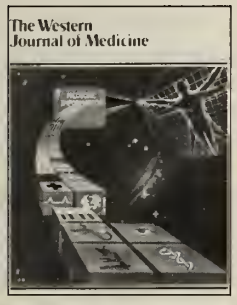
The special issue editor for *Women and Medicine* is Linda Hawes Clever, MD—Doctor Clever is chair of the Department of Occupational Health at Pacific Presbyterian Medical Center in San Francisco.

IDS— Global erspective



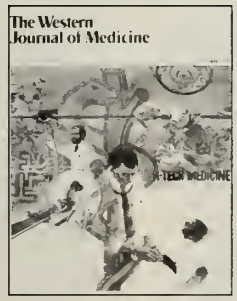
his issue, from . the World Health ganization, con- ers the methods l limitations of)S case reporting l HIV serologic dies, summarizes des of transmis- n, defines geo- phic patterns of ead, and examines epidemiology of / infections by con- nt. Jonathan M. nn, MD, Special ie Editor, 1987.

Medical Informatics



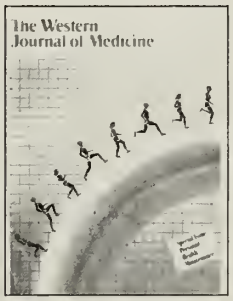
Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



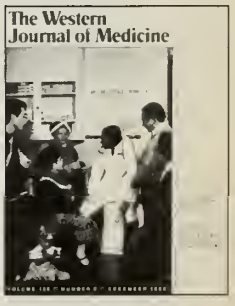
This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

Personal Health Maintenance



Personal Health Maintenance provides an authoritative guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology, and clinical medicine. John H. Holbrook, MD, Special Issue Editor, 1984.

Cross-cultural Medicine



Cross-Cultural Medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983.

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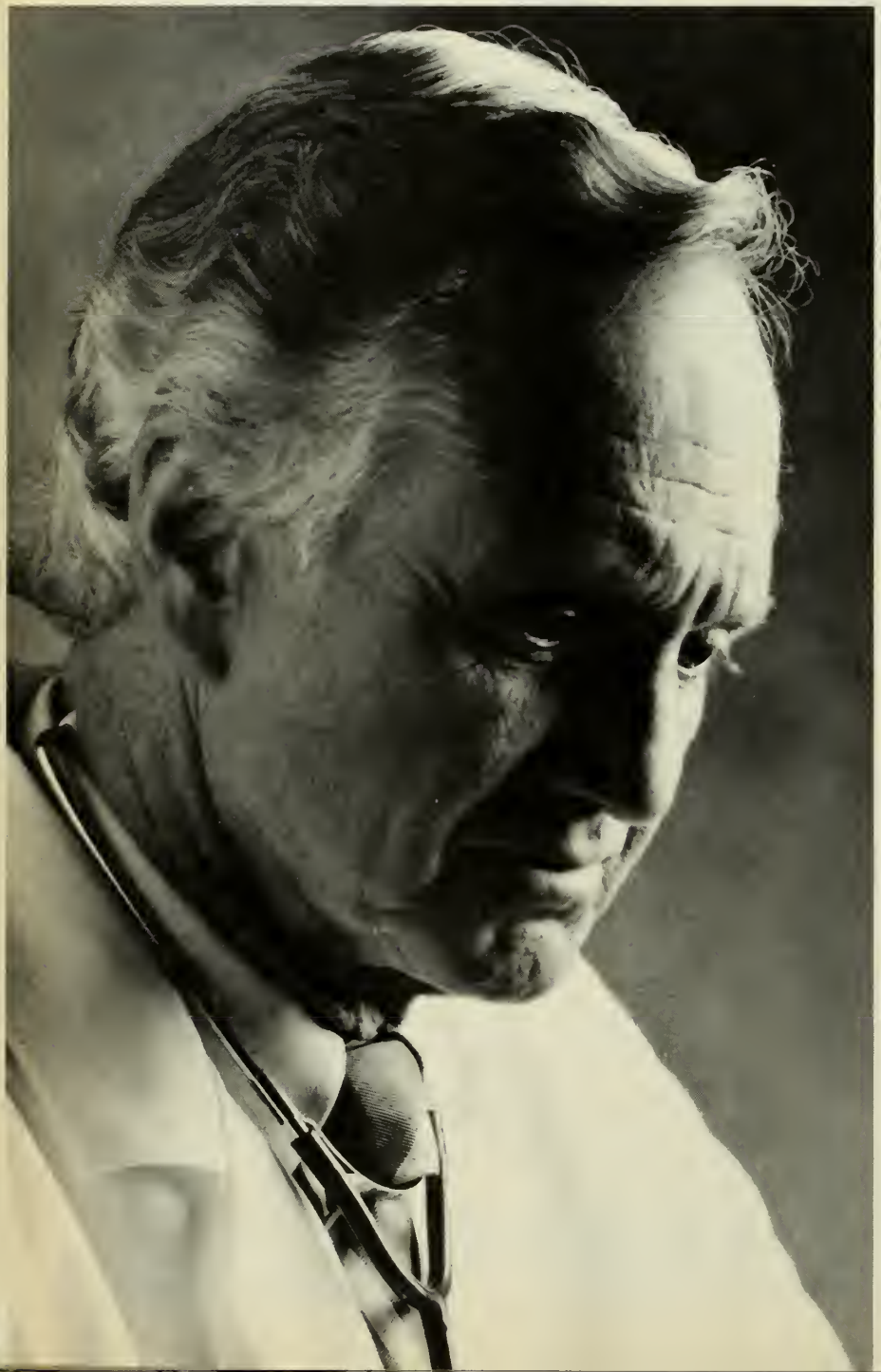

Few things elicit feelings of depression, rage, helplessness and exasperation as thoroughly as receiving suit papers for a malpractice claim. This physician suffered just such an unpleasant experience... but his odds of winning were better than most. Why? Because his professional liability insurance carrier is Insurance Corporation of America.

The circumstances of this claim could occur and have occurred in operating rooms and doctors' offices everywhere. A routine surgical procedure went sour when, for no apparent reason, the patient suffered a cardiac arrest. Prompt and proper attempts at resuscitation failed. Our physician was sued along with other

During discovery, information was released indicating the patient had previously undergone similar surgery under anesthesia *without* incident. Because of ICA's diligence and our willingness to exhaust all legal remedies, the jury was allowed to hear the autopsy report as well as the patient's past medical history. Those defendants who settled quickly never had an opportunity to present that evidence. And ultimately our insured was exonerated.

surgeons in the operating room, the primary care physician, the anesthesiologist and the hospital.

Subsequent to surgery, it was determined the patient had arrested as a result of an allergic reaction to the anesthesia. Unlike other carriers involved, who settled quickly to avoid costly "death incident" litigation, ICA recognized our physician was not at fault. Fortunately for him, ICA is dedicated to the strongest claims defense possible. And because ICA also understands that a doctor's most valuable asset is his reputation, protecting it becomes *our* bottom line.

So ICA and the doctor fought alone — and at ICA's expense. ICA in-house attorneys screened and selected local defense attorneys skilled in malpractice cases and familiar with the judicial climate of the region. Then, they planned strategy, investigated the facts, and monitored the defense.

What does this mean to the doctor? He leaves the courtroom with his reputation, his policy limits and his checkbook intact, all because of his partnership with ICA, where we put reputation, principles and dignity ahead of the quick fix. The reason why? Because ICA is people who *care*. Period.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 785)

March 16-19—**Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director of Medical Education, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

April 6-8—**Postgraduate Course in General Surgery.** UCSF at San Francisco Hilton. Thurs-Sat. Contact: UCSF.

May 20—**6th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic Surgery Medical Group at La Jolla Marriott Hotel. Mon. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 598-0080.

OF INTEREST TO ALL PHYSICIANS

December 24-30—**Advances in Medicine.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sat-Fri. 15 hrs. $400. Contact: Joe Harrison, MD, PO Box 10185, Lahaina, Hawaii 96761. (808) 661-8032.

January 17-21—**Intensive Course in Geriatric Medicine.** UCLA Multi-Campus Division of Geriatric Medicine at Beverly Hilton, Beverly Hills. Tues-Sat. 34 hrs. $265. Contact: Susan Vivell, UCLA Multi-Campus Division of Geriatric Medicine, Dept 32-144 CHS, Los Angeles 90024-1686. (213) 825-8255.

January 18—**16th Annual Respiratory Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

January 19-22—**Health Science Response to Child Maltreatment: 1989.** Children's Hospital & Health Center at Omni Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 20-22—**Urology and Gynecology for Primary Care Physicians.** UCSD at Hyatt Islandia Hotel, San Diego. Fri-Sun. 13 hrs. Contact: Edith S. Bookstein, UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Princess Resort. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 20-22—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at La Jolla Marriott. Fri-Sun. 18 hrs. $225. Contact: Bonny A. Mower, Conference Coordinator, Department of Academic Affairs, 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

January 27-29—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Bally's Grand Hotel, Las Vegas. Fri-Sun. Contact: Deborah Wilderson, Educational Coordinator, Division of CME, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

January 29-February 3—**Selected Topics in Family Practice.** Tropical Seminars at King Kamehameha Hotel, Kona, Hawaii. Sun-Fri. 20 hrs. Contact: Tropical Seminars, North Kitsap Medical Center, 20700 Bond Rd NE, Poulsbo, WA 98370-9099. (800) 441-4439.

February 1-4—**Recent Advances in Geriatric Medicine: Innovative Approaches to Quality Nursing Home Care: The Care Plan and Beyond.** UCSD at Catamaran Resort Hotel, San Diego. Wed-Sat. 17 hrs. $310. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121.

February 3—**Ionizing Radiation Safety.** USC. 2 hrs. Contact: USC. (213) 743-6383.

February 10-12—**58th Midwinter Clinical Conference.** Research Study Club at Moseley-Salvatori Conference Center. Fri-Sun. Contact: Research Study Club, PO Box J, South Pasadena 91030.

February 13-17—**Occupational Respiratory Protection.** USC. 3.5 hrs. Contact: USC. (213) 743-6523.

February 15-18—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 16-18—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and the Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Thurs-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

February 20-22—**9th Annual Betty Ford Center Conference on Alcoholism/Chemical Dependency: Perspective on Alcoholism Treatment: Ongoing Issues in Integrating the 12-Step Program.** Annenberg Center at Betty Ford Center at Eisenhower, Rancho Mirage. 13 hrs. Contact: Annenberg Center, Eisenhower Medical Center, 39000 Bob Hope Dr, Rancho Mirage 92270-3298. (800) 621-7322.

February 23-24—**Transportation of Hazardous Materials/Waste.** USC. 1.4 hrs. Contact: USC. (213) 743-6523.

February 25-March 4—**Update: Controversies in Emergency and Primary Care.** Scripps Memorial Hospital Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 27-28—**Back Injury Prevention.** USC. 1.4 hrs. Contact: USC. (213) 743-6523.

February 27-March 2—**Post Concussion Syndrome: Advances, Update and Review.** Centre for Neuro Skills and Southern California Neuropsychiatric Institute at Caesar's Palace, Las Vegas, Nevada. Mon-Thurs. 21 hrs. Contact: Sherry Ryan, SCNPI, La Jolla Blvd, La Jolla 92037. (619) 454-2102.

March 3-5—**Asia Pacific Alzheimer's Disease Conference.** Pacific Islands Geriatric Education Center at Hilton Hawaiian Village, Honolulu, Hawaii. Fri-Sun. 21 hrs. $300. Contact: Katherine Kim, Pacific Islands Geriatric Education Center, 347 N Kuakini St, Honolulu, HI 96817. (808) 523-8461.

March 5-8—**Asia-Pacific Osteoporosis Conference.** Kuakini Osteoporosis Center at Hilton Hawaiian Village, Honolulu, HI. Sun-Wed. 25 hrs. $450. Contact: Shirley Kuma, KOC, 347 N Kuakini St, Honolulu, HI 96817. (808) 547-9578.

March 8—**Veterinary Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

March 18-25—**Primary Care Medicine: Update '89.** UCSF at the Waiohoi, Kauai, Hawaii. 1 week. 20 hrs. $465. Contact: UCSF.

March 19-22—**Annual Meeting of the Society for Adolescent Medicine.** Society for Adolescent Medicine at San Francisco. Sun-Wed. Contact: Edie Moore, 10727 White Oak Ave, Ste 101, Granada Hills 91344. (818) 368-5996.

March 29-31—**Annual Review in Family Medicine: Pharmacotherapeutics in Primary Care.** USC at Stanford Court Hotel, San Francisco. Wed-Fri. 14 hrs. Contact: Department of Family and Community Medicine, 400 Parnassus Ave, A C9, San Francisco 94143-0900. (415) 476-5250.

April 8—**Antibiotics: 1989 and Beyond.** Grossmont District Hospital at Kona Kai and Tennis Resort, San Diego. Sat. 8 hrs. Contact: Verda Belyeu, CME Office, Grossmont Hospital, PO Box 158, La Mesa 92044. (619) 589-4153.

April 12—**Preventive Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

April 12-14—**39th Annual Course for Physicians in Family Practice: Family Practice Update 1989.** Mount Zion Hospital and Medical Center at San Francisco. Wed-Fri. $325. Contact: Family Practice Course, Mount Zion Hospital and Medical Center, PO Box 7921, San Francisco 94120. (415) 885-7270.

April 13-15—**Recent Advances in Hemophilia Care.** The Hemophilia Treatment Center Orthopaedic Hospital at Los Angeles Hilton. Thurs-Sat. $200. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

April 14-16—**Office Orthopaedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 29-30—**The Cutting Edge 1989 Erotic Mysteries: Resolving Obstacles to Intimacy.** UCSD at San Diego Marriott Hotel & Marina. Sat-Sun. 12.5 hrs. $295. Contact: Cass Jones, Meeting Management, 3770 Tansy St, San Diego 92121. (619) 453-6222.

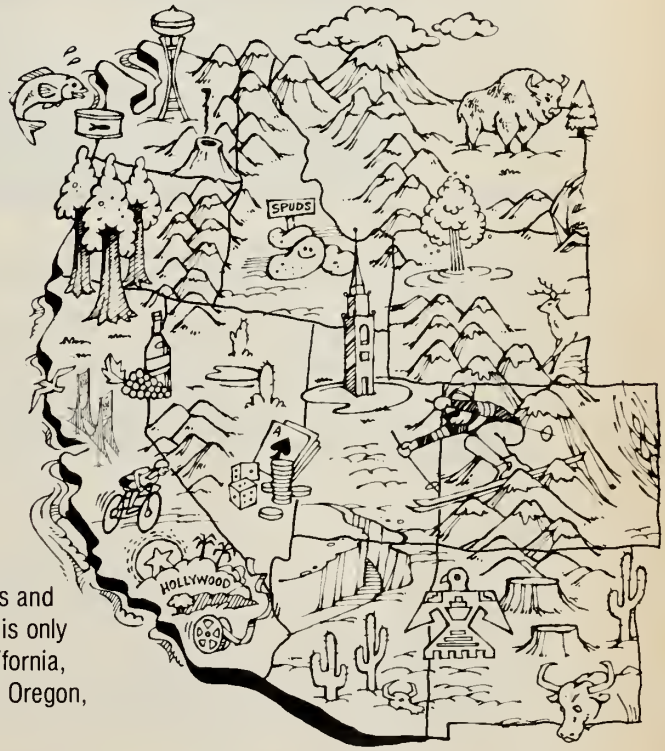
(Continued on Page 792)

The Western Journal of Medicine

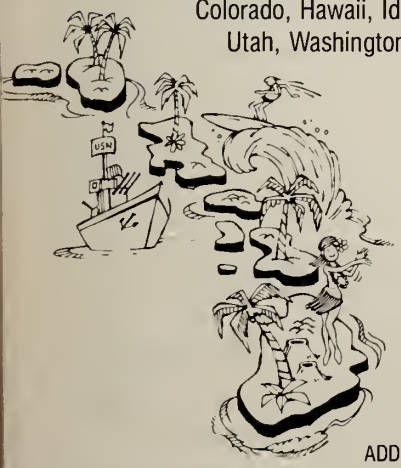
Medical Student 1989 Writing Award Competition

$1,000 CASH PRIZE!

■ Enter your original medical research or medical review article—the article must be of interest to clinicians and not previously published. The winner will receive a $1,000 cash prize and a two-year subscription to **The Western Journal of Medicine.** The winning article will be published in **WJM. Deadline to enter February 1, 1989.**



■ **WJM** is the official journal of eight western state medical associations and six clinical investigation/specialty societies. This competition open is only to medical students attending school in Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, or Wyoming.



■ **WJM** is clinically oriented, national in scope, and not confined to any single specialty. Your article must be written in **WJM** style and be of interest to our readers. If, in the judgment of the editorial board, no articles meet the standards of **WJM,** no award will be made.

ADDITIONAL RULES:

Articles must be 3,000 to 4,000 words in length. The manuscript must be identified as submitted for ısideration for this award.

Co-authorship is permitted if all authors meet the qualifications. The $1,000 award will be divided equally ong the co-authors.

Articles must conform to **WJM's** style—our style guide, "Information for Authors," appears in the January and / issues, or you may write our editorial department for a copy of the guide.

Articles will be judged by the editors and the editorial and advisory boards of the journal.

The winner will be announced and the article published in **WJM.** In case of a tie, the $1,000 award will be ded equally.

DEADLINE: FEBRUARY 1, 1989.

For additional information write to:

THE WESTERN JOURNAL OF MEDICINE
Editorial Office/Award Competition
P.O. Box 7602
San Francisco, CA 94120-7602

(Continued from Page 790)

April 30-May 3—**12th Annual National Conference on Rural Health: Redesigning Rural Health: Blueprints for Success.** National Rural Health Association at Bally's Hotel, Reno, Nevada. Sun-Wed. Contact: Robert Quick, Communications Director. (816) 756-3140.

May 10—**Laboratory Medicine Symposium.** Enloe Hospital and Chico Community Hospital at The Esplanade Building, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Medical Staff Office, Enloe Hospital. (916) 891-7300.

May 19-20—**Medical Consequences of Alcohol and Other Drugs.** UCSD. Thurs-Fri. 9 hrs. $105. Contact: UCSD.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 21-22—**Family Practice Winter Seminar.** Journal Center Pyramid Holiday Inn, Albuquerque. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

February 24-26—**17th Annual New Mexico Thoracic Society Lung Disease Conference.** Taos. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 217 Truman NE, Albuquerque 87108. (505) 265-0732.

March 1-4—**New Mexico Metabolism Symposium.** Quail Ridge Inn, Taos. Contact: Kathy Sikes, Lovelace Medical Foundation, 2441 Ridgecrest SE, Albuquerque 87108. (505) 262-7749.

March 2-4—**Santa Fe Ski Symposium—The Kidney in Systemic Disease.** Hotel Eldorado, Santa Fe. Contact: Pat Scott, National Kidney Foundation of NM, 1715 Girard NE, Albuquerque 87106. (505) 266-4573.

March 4—**Common Gastrointestinal Problems of Children.** UNM Nursing/Pharmacy Building, Room 135, Albuquerque. Contact: New Mexico Pediatric Society, UNM School of Medicine, Dept of Pediatrics, Albuquerque 87131. (505) 277-3967.

March 9-11—**Orthopaedic Surgery Conference.** Tammaron at Purgatory. Contact: Kathy Sikes, Lovelace Medical Foundation, 2441 Ridgecrest SE, Albuquerque 87108. (505) 262-7749.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 6-8—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). Fri-Sun. 15 hrs. Snowbird. Contact: (801) 581-8664.

January 12-14—**Arthroscopic Surgery** (Sponsor: UUMC). Thurs-Sat. Phoenician Resort, Scottsdale, Arizona. Contact: (801) 581-7601.

January 14-21—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). One week. Aston Genesis Resort, Park City. Contact: (801) 581-8664.

February 5-10—**A Practical Approach to Modern Chest and Musculoskeletal Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird. Contact: (801) 581-7553.

February 7-10—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Red Lion Inn, Salt Lake City. Contact: (801) 581-8635.

February 12-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. The Yarrow, Park City. Contact: (801) 581-8664.

February 22-25—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott. Contact: (801) 521-1311.

February 22-25—**Rigid Fixation and Craniofacial Anomalies** (Sponsor: UUMC). Wed-Sat. Snowbird. Contact: (801) 581-8664.

February 26-March 3—**A Practical Approach to Modern Chest and Musculoskeletal Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: (801) 581-7553.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
BYUHS:	Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.
DMC:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
SMH:	St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC:	University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.
UVRMC:	Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

(Continued on Page 794)

A BREAKTHROUGH
In Disability Insurance

NOW–A disability/income replacement program that insures you in your specialty...ends your premiums after 10 years...then gives you back up to 100% or more of your money upon retirement–or sooner!

You know you can't do without disability insurance. Though you doubt it'll happen, you *could* be disabled. And if so, who'll pay the bills? But you wince at paying out those high premiums with no build up of equity to cash in on later. With the coverage you need at your income level, it could be a lot of money down the drain.

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Address _____

City _____ State _____ Zip _____

Phone ( ) _____

CONTINUING MEDICAL EDUCATION

(Continued from Page 792)

March 1-4—**Update in Maternal Fetal Medicine** (Sponsor: UUMC). Wed-Sat. Contact: (801) 581-5501.

March 5-11—**Advances in Internal Medicine** (Sponsor: UUMC). Sun-Sat. Snowbird. Contact: (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 13—**Understanding Arrhythmias & Pacemakers: A Workshop for Practitioners.** Seattle. Fri. Contact: VMMC.

February 3—**Advances in Therapy of Hypertension.** Seattle. Fri. Contact: VMMC.

February 9-10—**Legal Aspects of Occupational Safety and Health.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

February 10-11, May 19-20, August 24-25—**MKSP Review Course, Parts 1, 2, 3.** Seattle. Fri-Sat. May: Fri-Sat. Aug: Thurs-Fri. Contact: VMMC.

February 27-March 1—**Current Issues in Infectious Disease.** Seattle. Mon-Wed. Contact: (206) 326-7349.

March 3—**Neurologic Complications of Systemic Disease.** Seattle. Fri. Contact: VMMC.

March 10—**Management of Problem Wounds.** Seattle. Fri. Contact: VMMC.

March 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: U/W, (206) 543-1069.

March 22-24—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

April 20-21—**Ergonomics.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

May 15-17—**Occupational Hazards to Health Care Workers.** Seattle. Mon-Wed. Contact: U/W, (206) 543-1069.

June 2—**Current Otology.** Seattle. Fri. Contact: VMMC.

July 10-12—**The Best Approach 1989: Sports Medicine.** Seattle. Mon-Wed. Contact: (206) 326-7349. ◆

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE AIDS PATIENT—AN ACTION AGENDA—Cornell University Medical College Fourth Conference on Health Policy—Edited by David E. Rogers, MD, Walsh McDermott University Professor of Medicine, New York Hospital-Cornell Medical College, and Eli Ginzberg, Director, Conservation of Human Resources, and A. Barton Hepburn Professor Emeritus of Economics, Columbia University, New York. Westview Press, 5500 Central Ave, Boulder, CO 80301, 1988. 155 pages; $24.95, hard cover; $10, paperback.

ANESTHESIA IN HEPATIC AND BILIARY TRACT DISEASE—Burnell R. Brown, Jr, MD, PhD, Professor and Head, Department of Anesthesiology, and Professor, Department of Pharmacology, University of Arizona Health Science Center, Tucson. F. A. Davis Company, 1915 Arch St, Philadelphia, PA 19103-1493, 1988. 281 pages, $58.

DIAGNOSTIC NUCLEAR MEDICINE—Second Edition—2 volumes—Edited by Alexander Gottschalk, MD, Professor and Chairman, and Paul B. Hoffer, MD, Professor and Chief of Nuclear Medicine, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut, and E. James Potchen, MD, Chairman, Department of Radiology, Michigan State University, East Lansing. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1988. 1,154 pages, $215.

EXPERIMENTAL SURGERY AND PHYSIOLOGY: INDUCED ANIMAL MODELS OF HUMAN DISEASE—Edited by M. Michael Swindle, DVM, Professor and Chairman, Department of Comparative Medicine, and Associate Professor, Department of Surgery, Medical University of South Carolina, Charleston, and Robert J. Adams, DVM, Associate Professor, Division of Comparative Medicine, The Johns Hopkins University School of Medicine, Baltimore, Md. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1988. 341 pages, $59.95.

INTENSIVE CARE—FACING THE CRITICAL CHOICES—Thomas A. Raffin, MD, Associate Professor and Assistant Chief of Medicine and Associate Director of the intensive care units, Stanford University Medical Center; Joel N. Shurkin, science writer, Stanford University; and Wharton Sinkler III, MD, anesthesiologist and Episcopalian minister. W. H. Freeman and Company, 41 Madison Ave, New York, NY 10010, 1989. 204 pages, $14.95.

MANUAL OF CLINICAL PROBLEMS IN NEPHROLOGY—Burton David Rose, MD, Associate Professor of Medicine, Harvard Medical School and Harvard Center for the Study of Kidney Diseases, and Director of Clinical Nephrology, Brigham and Women's Hospital, Boston, and Robert Mark Black, MD, Assistant Professor of Medicine, University of Massachusetts Medical School, and Director of Nephrology, The Fallon Clinic, Worcester, Mass. Little, Brown and Company, 34 Beacon St, Boston, MA 02108, 1988. 398 pages, $22.50 (spiralbound).

MATERNAL AND CHILD HEALTH PRACTICES—Third Edition—Edited by Helen M. Wallace, MD, MPH, Professor of Maternal and Child Health, Graduate School of Public Health, San Diego State University; George M. Ryan, Jr, MD, MPH, Professor, Department of Obstetrics and Gynecology, University of Tennessee College of Medicine, Memphis; and Allan C. Oglesby, MD, MPH, Professor and Head, Division of Maternal and Child Health, Graduate School of Public Health, San Diego State University. Third Party Publishing Company, PO Box 13306, Montclair Station, Oakland, CA 94661-0306, 1988. 722 pages; $29.95 to California addresses, $27.95 to other US states, $32.95 to other countries (paperback).

MEDICAL ETHICS AND THE ELDERLY: A CASE BOOK—Mark H. Waymack, PhD, Assistant Professor of Philosophy and Adjunct Assistant Professor of Medical Humanities, Loyola University of Chicago, and George A. Taler, MD, Assistant Professor of Family Medicine and Director, Division of Geriatrics, University of Maryland School of Medicine, Baltimore. Pluribus Press, Inc, 160 E Illinois St, Chicago, IL 60611, 1988. 248 pages, $29.95.

OTOLARYNGOLOGY—Problems in Primary Care—Richard W. Babin, MD, Professor and Chairman, Department of Otolaryngology, University of Tennessee, Memphis; Christopher J. Harrison, MD, Assistant Professor of Pediatrics, Division of Infectious Diseases, Children's Hospital Medical Center, Cincinnati; and D. Thomas Upchurch, MD, Clinical Assistant Professor, Department of Otolaryngology and Maxillofacial Surgery, University of Tennessee, Memphis, and Clinical Assistant Professor, Department of Surgery, University of Tennessee, Knoxville. Medical Economics Books, Oradell, NJ 07649, 1988. 333 pages, $42.95.

A POCKET MANUAL OF DIFFERENTIAL DIAGNOSIS—Second Edition—Stephen N. Adler, MD, Clinical Instructor in Medicine, University of Oklahoma College of Medicine, and Medical Director, Respiratory Therapy, Mercy Health Center, Oklahoma City; Mildred Lam, MD, Assistant Professor of Medicine, Case Western Reserve University School of Medicine, and Assistant Director, Hemodialysis Unit, Nephrology Division, Cleveland Metropolitan General Hospital; Dianne B. Gasbarra, MD, Clinical Instructor in Medicine, University of Oklahoma College of Medicine, and Internist and Pulmonary Disease Specialist, Mercy Health Center, Oklahoma City; and Alfred F. Connors, Jr, MD, Assistant Professor of Medicine, Case Western Reserve University School of Medicine, and Director, Medical Intensive Care Unit, Pulmonary Disease and Critical Care Division, Cleveland Metropolitan General Hospital. Little, Brown and Company, 34 Beacon St, Boston, MA 02108, 1988. 337 pages, $15 (paperback).

PREVENTION OF ADULT ATHEROSCLEROSIS DURING CHILDHOOD—Report of the 95th Ross Conference on Pediatric Research. Ross Laboratories, Columbus, OH 43216, 1988. 130 pages, $5.00 (paperback).

SCULPTURE—A MAN'S GUIDE TO COSMETIC SURGERY—Mark A. Mandel, MD, Plastic and Reconstructive Surgery, Los Angeles. PaperJacks, 210 Fifth Ave, New York, NY 10010, 1988. 229 pages, $4.50 (paperback).

SELLING OR BUYING A MEDICAL PRACTICE—Gary R. Schaub, MBA, Clinical Instructor in Practice Management, Oregon Health Sciences University, Portland. Medical Economics Books, Oradell, NJ 07649. 178 pages, $31.95.

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FAMILY PRACTICE/URGENT CARE PHYSICIAN, BC/BE to staff Immediate Care Center of 35 physician multispecialty clinic in southeastern Washington. Excellent compensation and benefit package. Send CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

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WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available in all specialties with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; 1 (800) 544-1987.

SACRAMENTO. BC/BE Family Physicians needed for full-time primary care clinic, part-time ER/part-time primary care clinic, or full-time in our ER. We are a large-staff model HMO offering competitive salary, excellent benefit package, and shareholder status. California license required. Contact Richard Fury, MD, 1001 Riverside Ave, Roseville, CA 95678 or call (916) 784-4620. EOE.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St Southwest, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

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CRESCENT CITY, CALIFORNIA. Exciting position available at a growing 24,000 visit ER in a rural, coastal community. Fee-for-service with possibility of six figure income. Send CV to Art B. Wong, MD, FACEP, EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

SACRAMENTO, CALIFORNIA. Family Practitioners and Internists needed part-time for staffing ambulatory care clinic. Our clinic operates seven days a week during days and evenings and provides episodic care on a same-day basis. Physicians may choose to work one to 10 half-days or evenings per week with wide flexibility. Full benefits and retirement if working six or more half-days a week on a steady basis. Please call John Petitt, MD, (916) 973-5560 or send CV to John Petitt, MD, The Permanente Medical Group, Inc, 3240 Arden Way, Sacramento, CA 95825.

OB/GYN. San Francisco bay area prepaid medical group with new LDR suite and family centered Obstetrical practice as well as full Gynecological practice has opening with competitive salary and generous benefit package. Send CV to Mary Ann Miner, MD, Chief, OB/GYN Department, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063.

GENERAL INTERNISTS. BC/BE General Internists needed for multispecialty group. We are experiencing robust growth and are seeking Internists to join large established Department of Medicine with University affiliation. Our hospital provides integral part of University of California, Davis housestaff training program. Pleasant outpatient practice setting is in six to nine physician modules. Excellent starting salary with rapid early advancement and steady yearly salary growth thereafter. Full benefits and retirement. This is an outstanding practice opportunity. Please call Dennis Ostrem, MD, Chief of Medicine, The Permanente Medical Group, Inc, (916) 973-5781 or send CV to Dennis Ostrem, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825.

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INTERNIST WANTED. Dynamic, expanding Beverly Hills area group seeks two Internists capable of giving high quality, compassionate care to good mix of fee-for-service/managed-care patients. Congenial group offers competitive salary, medical/dental/malpractice/disability package, profit-sharing, and partnership potential. Respond with CV to Medical Group of Beverly Hills, 5901 W. Olympic Blvd, Ste 201, Los Angeles, CA 90036, Attn: Medical Director.

SURGICAL ONCOLOGIST. A position is available for a well trained Surgical Oncologist to join an established multidiscipline group in Long Beach, California. Please send CV to PO Box 30, Long Beach, CA 90801.

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(Continued on Page 796)

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The minimum qualifications for entrance to this examination are possession of a valid California medical license or an Osteopathic Examiners license. Five years of recent experience in the general practice of medicine or in one of the specialty areas including two years in one, or a combination of the following:

(a) membership in a Medical Records Review or Utilization Committee at a national, state, county or an approved hospital level; (b) member of the State Board of Medical Quality Assurance; (c) member of a formal body charged with the review of standards or criteria of medical care.

(A master's degree involving public policy or public health orientation may be substituted for the two years of specialized experience pending State Personnel Board Approval.)

A State Application (Form 678) must be received by January 5, 1989. Any application received after that date will not be accepted. All applications will be screened and *only* those qualified will be invited to participate in the oral interview. Send a state application and CV to **Department of Consumer Affairs, Examination Unit, 1020 N St, Room 535, Sacramento, CA 95814; (916) 324-6513; Attention: Susan Cady.**

OREGON COAST. Busy fee-for-service multispecialty group looking for additional Internist and Family Practitioner including OB to work with two Internists and three Family Practice Physicians. Well-equipped clinic next to 34-bed hospital with eight ICU/CCU beds and two new birthing rooms. Top-notch school system and just 75 miles to Portland. Send CV or call Rick Bigger at North Coast Medical Center, PC, 727 Wahanna Rd, Seaside, OR 97138; (503) 738-9551.

INTERNIST. Needed to establish a group practice in Redding, California. Excellent opportunity leading to a partnership. First year salary guaranteed. Must be BE/BC in Internal Medicine. Use all of your hospital and consultative skills in an area not overcrowded by subspecialists. Progressive hospital with open heart program and active ICU/CCU. Send CV to 2240 Court St, #B, Redding, CA 96001.

EMERGENCY MEDICINE GROUP seeking career oriented ACLS, ATLS physician for immediate opening. Moderate volume; income $140,000. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to KEP, PO Box 6192, Kennewick, WA 99336; or call (509) 627-1798.

RHEUMATOLOGIST. Immediate opening for BC/BE Rheumatologist with large prepaid group practice in San Francisco bay area. Busy clinical practice with opportunities for teaching and research. University appointment possible. Competitive salary. Generous benefit package. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, Permanente Medical Group, 260 International Cir, San Jose, CA 95119 or phone (408) 972-6560.

PHYSICIANS WANTED

GENERAL PRACTICE. Busy medical center needs full-time physicians for urgent appointments. Significant evening and weekend hours. Abundant free time with no on-call responsibility. Excellent benefits and retirement program. Kaiser Permanente, Santa Teresa Hospital, 250 Hospital Parkway, San Jose, CA 95119; (408) 972-6180.

PALO ALTO, CALIFORNIA. Family Physician BC/BE to join nine-member department in large multispecialty group. Highly desirable location; excellent benefits. Clinical faculty appointment at Stanford available. Contact Susan D. Smith, MD, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

INTERNIST. San Francisco bay area HMO seeks BC/BE Internist to join dynamic multispecialty group. Excellent salary and fringe benefits. Send CV and references to Dr Michael Getzell, Kaiser Permanente, 27400 Hesperian Blvd, Hayward, CA 94545.

MODESTO, CALIFORNIA community clinic is recruiting a Primary Care Physician to serve farm workers and other underserved people, including the homeless. Excellent location in city of 180,000, one and one-half hours from Yosemite and the bay area. Please contact Michael Sullivan, Merced Family Health Centers, Inc, PO Box 858, Merced, CA 95341; (209) 383-1848.

DIRECTOR OF DIVISION OF NEUROSURGERY. Progressive BC/BE Neurosurgeon to reorganize the Division of Neurosurgery at a major trauma and teaching center. Should be eligible for academic appointment at a major medical school. Compensation is a combination of teaching and administrative pay plus fee-for-service. Contact Francis L. Comunale, MD, Medical Director, San Bernardino County Medical Center, 780 E. Gilbert St, San Bernardino, CA 92404.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three-five weeks paid vacation; seven paid holidays; malpractice, medical, dental and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall 1988. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

SAN FRANCISCO BAY AREA multispecialty group seeks Neurologist, BC/BE, to join 24 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

SAN FRANCISCO BAY AREA multispecialty group seeks Internist, BC/BE, to join 24 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

WELL ESTABLISHED HMO located in northern California wine country seeking General Internists. Attractive salary, benefits, and security. Please send CVs to Rich Zweig, MD, 401 Bicentennial Way, Santa Rosa, CA 95403.

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Rapidly expanding 10-physician multispecialty group in new 15,000 square foot medical office seeks experienced medical director with BC in primary care or surgical specialty, strong HMO, UR, and committee background. Clinical 75%, administrative 25%. Strong administrative support, well financed, FFS and HMO. Competitive salary, stipend, benefits, profit sharing, and early equity. Call or forward CV to:

Dr Gary L. Groves, Pres.
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12 N. Fifth St
Redlands, CA 92373
(714) 825-4401

INTERNIST/NEPHROLOGIST with special interest in teaching Internal Medicine for full-time appointment in university-affiliated, active teaching and clinical program with part-time Nephrology private practice. Inquiries, including CV, should be sent to A. G. Kavalich, MD, Director, Nephrology, San Bernardino County Medical Center, 780 E. Gilbert St, San Bernardino, CA 92404.

OREGON COAST. BC/BE Family Practice Physician to join four Family Practitioners in multispecialty group. Full spectrum of Family Practice, optional OB. New clinic near hospital. Contact Mrs Jackie Crowder, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151 ext 294, or 1 (800) 234-1231.

NORTH IDAHO. Family Physician needed to join four physician group. College and two state universities within the locality. Area provides abundant outdoor recreational opportunities. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501.

SIX PHYSICIAN PRIMARY CARE GROUP seeks BC/BE Cardiologist for invasive/noninvasive practice in vacation community on Puget Sound. Practice located adjacent to community hospital, which is affiliated with Virginia Mason Medical Center in Seattle. Send CV to Harold R. Clure, MD, Fidalgo Medical Associates, PS, 24th and M Ave, Anacortes, WA 98221; or call (206) 293-3101.

PATHOLOGIST, APCP, desired for aggressive three man group with demanding, busy, interesting practice. Must have or be willing to rapidly develop a forte in Microbiology. Pacific/Rocky Mountain Northwest with abundant outdoor activities and competitive income. Please reply to Number 123, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

HEMATOLOGIST/ONCOLOGIST, WASHINGTON STATE BC/BE. Immediate opportunity to take over established practice within the Hematology/Oncology (three and one-half physician) Division of the Rockwood Clinic, a 60 member multispecialty group. Competitive salary and benefits leading to early shareholder status. Spokane (metropolitan population 350,000) offers affordable housing, excellent schools, cultural activities, and unlimited outdoor recreation. Send CV to Colleen Mooney, Recruitment Coordinator, Rockwood Clinic, TAF C-13, Spokane, WA 99220-4013; (509) 448-1304.

(Continued on Page 798)

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AIR FORCE

(Continued from Page 796)

PHYSICIANS WANTED

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Prestigious Chicago-based clinic group specializing in the treatment of venous disorders is expanding nationally. Our newest clinics in Beverly Hills and Costa Mesa are in need of physicians trained in internal medicine—or who have a broad base of medical experience. We will provide complete training in the latest proprietary techniques of treating venous disorders. We offer a six figure salary and bonus potential, along with malpractice insurance and health benefits. And since there are no weekend hours and a 40-hour work week, you will have plenty of leisure time. You won't have to worry about soliciting for patients or fighting insurance companies.

This is an outstanding opportunity for professional and financial advancement. If you are motivated to build a rewarding practice with the leader in the treatment of venous disorders, send your resume to:

Medical Director

Vein Clinics of America

2340 S. Arlington Heights Road
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FAMILY PRACTICE/SACRAMENTO. Due to continued growth, positions for Family Practice are now available at Kaiser Permanente Medical Center, south Sacramento. Our salary is very competitive and we have an outstanding retirement and benefits package. Your practice at Kaiser will allow insulation from the headaches and financial uncertainty of private office practice, while fostering your professional growth at a first rate medical center. For further information, please contact Jack Berger, MD, Assistant Chief, Department of Medicine, Kaiser Permanente Medical Center, 6600 Bruceville Rd, Sacramento, CA 95823; or call (916) 686-2267.

PACIFIC NORTHWEST—INTERNIST. There are three busy solo Internists, practicing near our 155-bed hospital in Tacoma, Washington, who are seeking associates. They prefer candidates with interest in Geriatrics. Send your CV to Manager, Professional Relations, Humana Inc, Dept HH-12, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

SAN FRANCISCO BAY AREA multispecialty group seeks Family Practitioner, BC/BE, to join 24 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

PHYSICIANS WANTED

OCCUPATIONAL/FAMILY PRACTICE. The Pacific Northwest's leading outpatient medical provider has career opportunities for Primary Care Physicians to join an expanding 150 person medical group. Full/part-time openings throughout California and Seattle-Tacoma, Washington. Prior outpatient/occupational experience preferred. Attractive package includes competitive base salary plus incentive program, malpractice insurance, comprehensive benefits, 401(k) plan, vacation/sick/holiday/CME. Opportunity for advancement for energetic, hard-working physician committed to quality health care. Join our dynamic team of health care professionals. Contact Robin Smith, Director, Personnel, Readi-Care/CHEC, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (408) 737-8531, (800) 237-3234.

FIVE PERSON INTERNAL MEDICINE GROUP seeking BC/BE Pulmonologist, intensive care bronchoscopy training. Sierra Foothills, California. Reply to Number 122, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEUROLOGIST, BC/BE, full/part-time, for expanding San Francisco bay area private practice with emphasis on Occupational Neurology and med-legal evaluations. Expertise in EMG, EEG, and EP desired. Excellent reputation, referral base, facilities, and support staff. CV and letter stating professional goals, availability to 4017 24th St, Ste #7, San Francisco, CA 94114.

SONOMA AND LAKE COUNTIES. Immediate openings for Emergency Physicians who desire to live in the wine country north of San Francisco. Prefer BC/BP Emergency Physicians, but will consider BC in Family Practice, Internal Medicine, or Surgery in conjunction with Emergency Medicine experience. Low/moderate volume ED's or in combination with satellite ACC. Guaranteed $90-$100,000 per year; paid malpractice. Contact Richard Gillespie, MD, Redwood Empire EM Group, PO Box 2467, Santa Rosa, CA 95405; (707) 546-4199.

INTERNISTS AND CARDIOLOGIST for busy, expanding, well-established multispecialty HMO with adjacent hospital. Liberal fringe benefits, competitive salary. Send CV to Mark Cole, MD, Permanente Medical Group, 1200 El Camino Real, South San Francisco, CA 94080.

RHEUMATOLOGIST. BC/BE wanted to join solo certified Rheumatologist with group coverage in large southern California private-pay Rheumatology practice. Salary plus bonus with association and investment opportunity. Lab, x-ray, and physical therapy. Clinical research and teaching opportunities. Send CV to R. S. Gordon, MD, FACP, Arthritis Medical Clinic, 5945 Brockton Ave, Riverside, CA 92506; or call (714) 781-7700.

FAMILY PRACTICE OR INTERNIST to associate with busy family practice in Tulare, California. Large office established for 30 years with x-ray, lab, etc. Excellent living and practice environment. (209) 686-8611.

SUN VALLEY—Internist to practice Primary Care with two Internists in quality multispecialty group. Well equipped hospital. High quality of life with outstanding year 'round recreation presents unique opportunity and professional challenge. CV and references with first letter please. Tom Peterson, PO Box 66, Sun Valley, ID 83353-0066; (208) 622-4526.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

PHYSICIANS WANTED

WALK-IN CLINIC CHICO, CALIFORNIA

Personable, motivated Primary Care Physician needed for full-time position. Practice located in Chico, a college city with a service area of 80,000. Close to all types of outdoor recreation. 90 minutes from Sacramento. Generous guarantee initially, with incentives. Malpractice paid. Health insurance provided. Call or write Thomas Neuschatz, MD, 620 Mangrove Ave, Chico, CA 95926; (916) 345-7800.

BC/BE NEUROLOGIST to join progressive San Francisco bay area HMO. Busy clinical practice in desirable Marin County. Competitive income and excellent benefits. Please contact Jonathan Freudman, MD, Assistant Chief, Department of Internal Medicine, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903. AA/EOE employer.

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee for service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

ORTHOPEDIST. One day per week. Medical-legal evaluations for traumatic injury patients. No surgery. California license required. Lucrative fee for service with high growth potential and guaranteed base. Contact Director, PO Box 14046, San Francisco, CA 94114.

LOS ANGELES (Los Angeles County)—55 physician multispecialty Medical Group seeks full-time BC/BE Physicians in the following specialties: Cardiology, ENT, Family Practice, Infectious Disease, and Rheumatology. Please send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004; (213) 386-8440.

VENTURA (Ventura County). Multispecialty group of 40 physicians has immediate position available for BC/BE Internist/Pulmonologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist/Pulmonologist, 2705 Loma Vista Rd, Ventura, CA 93003.

VENTURA (Ventura County). Multispecialty group of 40 physicians has immediate position available for BC/BE Cardiologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Cardiologist, 2705 Loma Vista Rd, Ventura, CA 93003.

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for two BC/BE Family Practitioners to join a growing department. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU, but no Obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1550 Gateway Blvd, Fairfield, CA 94533; (707) 427-4000.

FAMILY PRACTICE, PUGET SOUND. 23 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to Carol Larsen, Acting Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

(Continued on Page 800)

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More vulnerable to infection in smokers and older adults

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For respiratory tract infections due to susceptible strains of indicated organisms.

Summary.
Consult the package literature for prescribing information.

Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae, Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
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Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.
Administer cautiously to allergic patients.
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.
Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea), 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever): 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia.

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IMMEDIATE OPENING EXCELLENT SOUTHERN CALIFORNIA OB/GYN POSITION

In one of the most prestigious, desirable, and fastest growing coastal communities in northern Orange County.

Solo practitioner seeking motivated OB/GYN Physician to join highly successful, private practice with long-term partnership opportunity.

Superb guaranteed package with full range of benefits to include malpractice insurance and CME training.

Send Inquiries and Curriculum Vitae to:

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Physician Recruiters
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Beverly Hills, CA 90211

(213) 277-7331
(800) 922-7PHY

VENTURA COUNTY. Multispecialty group of 40 physicians has immediate positions available for two BC/BE Family Practitioners. These openings are located in the main facility in Ventura and the Camarillo and Oxnard satellite offices. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Family Practitioner, 2705 Loma Vista Rd, Ventura, CA 93003.

PEDIATRICIAN. Extraordinary practice opportunity for BC/BE Pediatrician to join busy practice in northern California coastal city. Salary first year, then partnership if mutually agreeable. Contact C. Cody, MD, 2800 Harris St, Eureka, CA 95501; (707) 445-8416.

FREE-STANDING EMERGENCY AND GENERAL MEDICAL CENTER in northern California college town seeks Physician with Emergency Room/Family Practice experience. Very attractive compensation. Contact Roy Grossman, MD, (916) 891-1676.

SAN MATEO COUNTY (SAN FRANCISCO BAY AREA). PHYSICIAN II PH. Immediate, new opportunity for a Primary Care Physician providing clinical/administration and policy development direction for the San Mateo County Correctional System. Supervise Physicians/Nurse Practitioners and Nurses while providing health care for 1,200 plus inmates at seven facilities. Opportunities for community liaison, health education, and future planning. Competitive salary and excellent benefits. Send CV to Bonnie Jones, Human Resources, 590 Hamilton, Redwood City, CA 94063; or call (415) 363-4340.

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Requirements for General Practitioner Surgeon who can do Family Practice: five years in General Practice and have general medical privileges in a recognized approved hospital in the United States. In the same hospital you will have intermediate and minor surgical privileges. A capability in the practice of Orthopedics is desirable.

Requirements for the Staff Physician indicate the need for a strong background in Obstetrics. Two years post-graduate training in Obstetrics and three years successful practice in Obstetrics/Gynecology are necessary. Can substitute two years practice for one year of training. Also requires full Obstetrical privileges in a recognized and approved hospital in the United States. Minor and intermediate surgical privileges are desirable as is an interest in the practice of General Medicine. U.S. or RMI citizenship required. Equal Opportunity Employer, M/F/V/H.

PHYSICIANS WANTED

SAN MATEO COUNTY (SAN FRANCISCO BAY AREA). PHYSICIAN III. Excellent opportunity for Primary Care Physician to run child and maternal health public health organization. Administer family planning, well baby clinics, etc., to county residents. Competitive salary and excellent benefit package. Contact Bonnie Jones at (415) 363-4340 or send CV to Ms Jones at Human Resources, 590 Hamilton, Redwood City, CA 94063.

FAMILY PRACTITIONER. Good salary, excellent outdoor recreation, low pressure. Join a two doctor group practice with guaranteed salary and all other costs paid. Live in rural town with hospital, near large city. Call (collect) or write Harvey Mullinix, Health West, Inc, PO Box 2377, Pocatello, ID 83206; (208) 232-7862.

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PEDIATRICIAN OR PEDIATRICIAN/NEONATOLOGIST. Multispecialty medical group seeks full-time BC/BE Pediatrician or Pediatrician/Neonatologist. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

OBSTETRICIAN/GYNECOLOGIST. Multispecialty medical group seeks full-time BC/BE Obstetrician/Gynecologist to join four other specialists. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

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(Continued on Page 801)

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UNIVERSITY OF WYOMING, STUDENT HEALTH SERVICE. The Student Health Service has openings for two Physicians: one 12-month full-time position; one nine-month (170 day) academic year position. Applicants must be BC in Family Practice or Internal Medicine and have approved resident training or have extensive practice experience. Applicant must be licensed in the State of Wyoming or be eligible for licensure and have at least four years of primary care experience. Physicians to join two full-time Physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, and pharmacy. Salary commensurate with qualifications and experience. The University of Wyoming is an Equal Opportunity/Affirmative Action Employer. Send CV to Thomas E. Cronkleton, MD, Acting Director, Student Health Service, University of Wyoming, PO Box 3068, Laramie, WY 82071. Closing date is January 18, 1989.

INTERNAL MEDICINE DEPARTMENT CHAIRMAN. Maricopa Medical Center of Phoenix, Arizona, is seeking a chairman for its Department of Internal Medicine. We seek a well-qualified individual with recognized credentials in medical education, patient care, and research. Vigorous leadership abilities are required. Duties will include active supervision of the residency and fellowship training programs. The candidate must be BC in Internal Medicine. Maricopa Medical Center is an Equal Opportunity Employer. Those interested should submit inquiries and CV to J. Kipp Charlton, MD, Chairman, Medicine Chairman Search Committee, Maricopa Medical Center, PO Box 5099, Phoenix, AZ 85010.

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VA MEDICAL CENTER, PRESCOTT, ARIZONA is recruiting for a BC Psychiatrist with administrative ability to function as Chief of Psychiatry Service. Salary range is $70,000 to $80,000 depending on qualifications. Prescott is a 200-bed medical facility with an active Alcohol Dependency Treatment Program. Prescott is located in the north central mountains of Arizona with a population of 25,000. Send CV to **F. C. Lepperd, Jr, MD, Chief of Staff, VA Medical Center, Prescott, AZ 86313; or call (602) 445-4860 ext 301.** Equal Opportunity Employer.

WOFFORD HEIGHTS (FAMILY PRACTICE). Fantastic opportunity for the right Physician! New 7,000 square foot multispecialty clinic opening in January 1989. Located in the beautiful mountain lakeside resort community of Wofford Heights, California, an hour east of Bakersfield, this facility will have office and exam space for four Physicians. Included will be a Pharmacy, full lab, x-ray services. Excellent salary and benefit package. No investment by the Physician. Malpractice paid in full. This is a rare opportunity to combine a very attractive lifestyle and an excellent practice opportunity. We are seeking to contract four Physicians now. Call George Johnston, (805) 845-3731 for details or write PO Box 457, Lamont, CA 93241.

PHYSICIAN. San Ysidro Health Center, a comprehensive multispecialty clinic, seeks Internist. Will perform outpatient and in-patient acute care services and handle all Nephrology patients. Training in Nephrology and two years experience as an Internist. Must be bilingual in English and Spanish. $62,400 per year. Send résumé to San Ysidro Health Center, Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073.

EUGENE, OREGON. Family Physicians, BE/BC, sought to join growing 36 Physician Family Practice/Internal Medicine group in Eugene and nearby rural Cottage Grove. OB optional. Excellent OB support available. Initial income guarantee with incentive. Partnership anticipated after two years. Outstanding schools. Abundant cultural and recreational opportunities. Please send CV or call Rob Daugherty, MD, Oregon Medical Group, 78-A Centennial Loop, Eugene, OR 97401; (503) 688-9140.

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CALIFORNIA, NORTHERN. A stable group of four ABEM Certified/Eligible MDs at coastal hospital of 24,000 patient visits would like two new associates. Income $60-$75 per hour. Will consider Family Practice but prefer Emergency Department trained Emergency Physician. Coastal paradise near redwood national parks, minutes from Klammath, Rouge, and Smith Rivers. Video tape of area available. Send CV to EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

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PEDIATRICIAN. County-sponsored, 17 physician multispecialty group practice with three satellite locations is looking for a BC/BE Pediatrician to provide primary and preventive health care services. Committed to high quality care. Comprehensive benefit package includes malpractice insurance coverage. Consider a semi-rural lifestyle with cultural amenities; easy access to metropolitan areas, the Sierra Nevadas, and the Pacific Ocean; lower housing costs (median price $75,000); and excellent schools. Salary: $76,536-$93,365 annually. Send CV to Michael L. MacLean, MD, Hillman Health Center, 1062 S. "K" St, Tulare, CA 93274; (209) 688-2015. Equal Opportunity Employer.

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PHYSICIAN. San Ysidro Health Center, a comprehensive multispecialty clinic, seeks Internist. Will perform outpatient and in-patient acute care services and handle Cardiology patients. Training in Cardiology and two years experience as an Internist. Must be bilingual in English and Spanish. $62,400 per year. Send résumé to San Ysidro Health Center, Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073.

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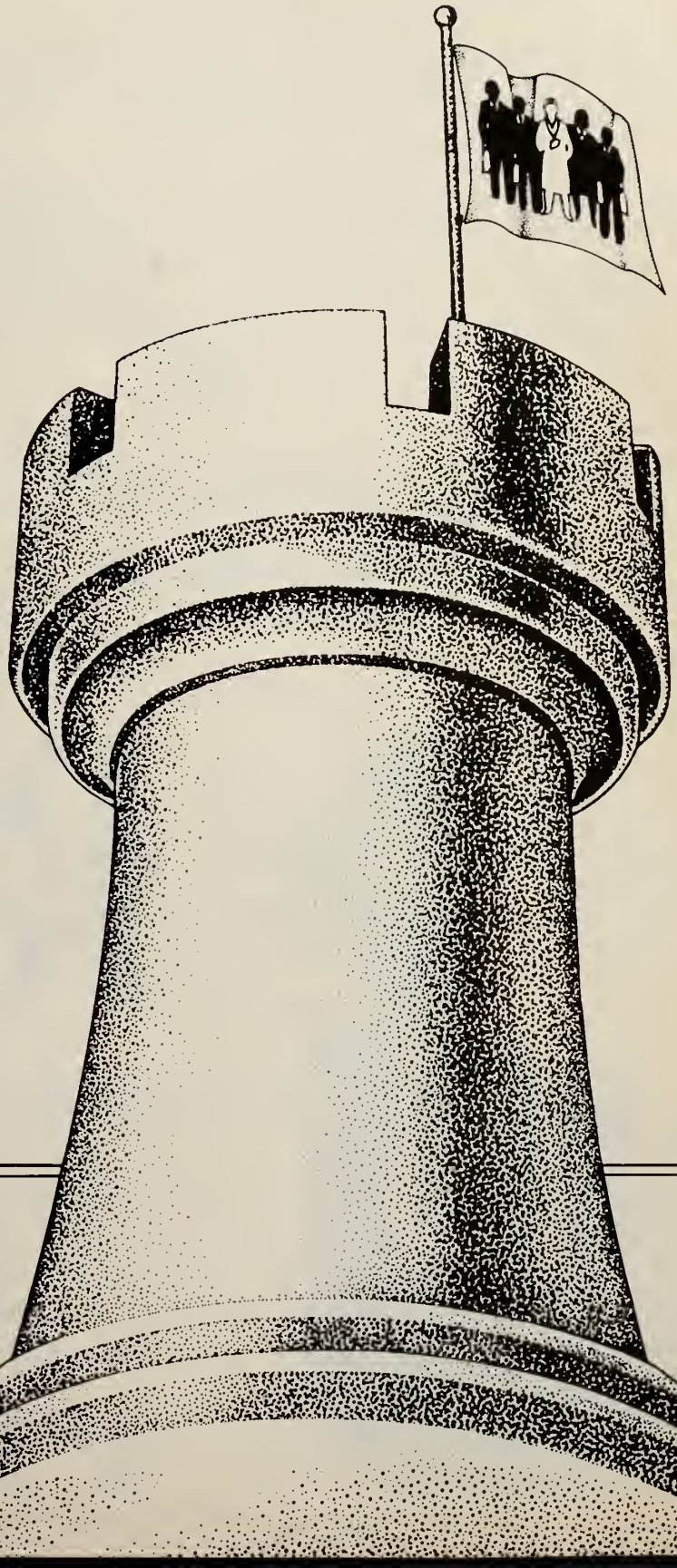

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 1-3, 1989, Pointe at South Mountain, Phoenix.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1989, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1989, date and place to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1989, date and place to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1989, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1989, date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: June 1-4, 1989, Ely.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 11-14, 1989, Holiday Inn Pyramid, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1989, date and place to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1989, date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1989, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1989, date and place to be announced.

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Before prescribing, please consult complete product information, a summary of which follows

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides; documented megaloblastic anemia due to folate deficiency; pregnancy at term and during the nursing period; infants less than two months of age.

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice, may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Perform complete blood counts frequently.

BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin.

PRECAUTIONS: *General:* Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (*e.g.*, elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.

Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, *e.g.*, impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).

Use in the Treatment of Pneumocystis Carinii Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, elevated aminotransferase (transaminase) values, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonia reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.

Information for Patients: Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.

Laboratory Tests: Perform complete blood counts frequently; if a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

Drug/Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. *Mutagenesis:* Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. *Impairment of Fertility:* No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism; use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects: See CONTRAINDICATIONS section.

Nursing Mothers: See CONTRAINDICATIONS section.

Pediatric Use: Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).** *Hematologic:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. *Allergic Reactions:* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periarteritis nodosa and systemic lupus erythematosus have been reported. *Gastrointestinal:* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. *Genitourinary:* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. *Neurologic:* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. *Psychiatric:* Hallucinations, depression, apathy, nervousness. *Endocrine:* Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. *Respiratory:* Pulmonary infiltrates. *Musculoskeletal:* Arthralgia, myalgia. *Miscellaneous:* Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN: *Usual adult dosage* for urinary tract infections is one DS tablet, two tablets or four teaspoonfuls (20 ml) *b.i.d.* for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis. *Recommended dosage for children* with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. *Renal Impaired:* Creatinine clearance above 30 ml/min, give usual dosage; 15-30 ml/min, give one-half the usual regimen; below 15 ml/min, use not recommended.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: Usual adult dosage is one DS tablet, two tablets or four teasp. (20 ml) *b.i.d.* for 14 days.

PNEUMOCYSTIS CARINII PNEUMONIA: Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

HOW SUPPLIED: *DS (double strength) Tablets* (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets* (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 100 ml and 16 oz (1 pint). *Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 16 oz (1 pint).

STORE TABLETS AT 15°-30°C (59°-86°F) IN A DRY PLACE PROTECTED FROM LIGHT. STORE SUSPENSIONS AT 15°-30°C (59°-86°F) PROTECTED FROM LIGHT.

P1. 028B

Roche Laboratories
a division of Hoffmann-La Roche Inc.
340 Kingsland Street, Nutley, New Jersey 07110-1199

"The Power of the Pen"

When you decide to use Bactrim, use the power of the pen as well. Protect your prescribing decision in accordance with your state regulations to prevent substitution. It guarantees your patients will get the power of Bactrim.

"Specify *Dispense as written*"

Bactrim™
(trimethoprim and sulfamethoxazole/Roche)

Roche Laboratories
a division of Hoffmann-La Roche Inc.
340 Kingsland Street, Nutley, New Jersey 07110-1199

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For urinary tract infection

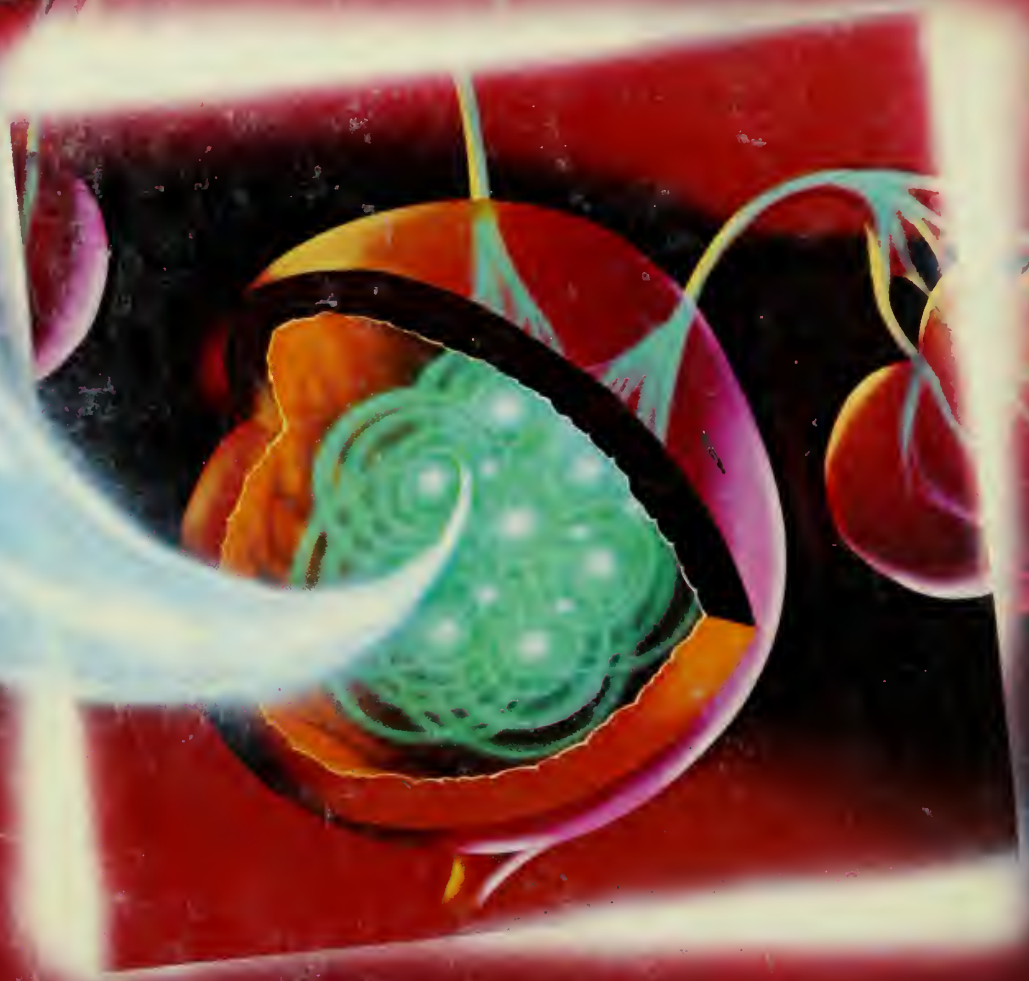

Illustration of Bactrim power in urinary tract infection.

Bactrim Power

- Penetrates
- Concentrates
- Overpowers
- Persists

Bactrim penetrates all tissues[1] to overpower most common susceptible uropathogens including *E. coli, Klebsiella* species, *Enterobacter* species, *Morganella morganii, Proteus (in vitro)* year after year.[2] B.i.d. dosing, easy transition from IV to oral, and economy help keep successful therapy within your power. Especially when you remember to protect your prescribing decision by specifying D.A.W.

Please note that *in vitro* data may not correlate with clinical experience. Bactrim is contraindicated in infants less than two months of age, in pregnancy at term, during lactation, and in documented megaloblastic anemia due to folate deficiency. Maintain adequate fluid intake.

Specify *"Dispense as written"*

Bactrim™ DS

(160 mg trimethoprim and 800 mg sulfamethoxazole/Roche)

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Please see references and summary of product information on adjacent page.

ROCHE®

Specify "Dispense as Written," "Do Not Substitute," or "Brand Necessary" according to your state regulations.